2-22-95

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: United States Patent No. 4,470,972	:	
Inventors: Elijah H. Gold, Bernard R. Neustadt and Elizabeth M. Smith	:	Attn: Box Patent Ext.
Issue Date: September 11, 1984	:	

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. Sec. 156 and 37 C.F.R. Sec. 1.710-1.785, Schering Corporation ("Schering"), owner of the above-identified patent by virtue of an Assignment by Elijah H. Gold, Bernard R. Neustadt and Elizabeth M. Smith of their interests in the above-identified patent which was executed on December 3, 1982 and recorded in the United States Patent and Trademark Office ("USPTO") on January 28, 1983 at Reel:4088, Frame:257 (Exhibit IX) hereby requests an extension of the patent term of United States Patent No. 4.470,972. The following information is submitted in accordance with 35 U.S.C. Sec. 156(d) and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, Sec. 1.710 to 1.785 and follows the numerical format set forth in 37 C.F.R. Sec. 1.740:

(1) A complete identification of the approved product as by appropriate chemical and generic names, physical structure or characteristics:

The approved product is RENORMAX® (brand of spirapril hydrochloride monohydrate) oral tablets; the active ingredient in the approved product has the following chemical names:

7-[N-[1-(S)-Ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic Acid Hydrochloride Monohydrate; and

7-[N-(1-(S)-Carboethoxy-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic Acid Hydrochloride Monohydrate;

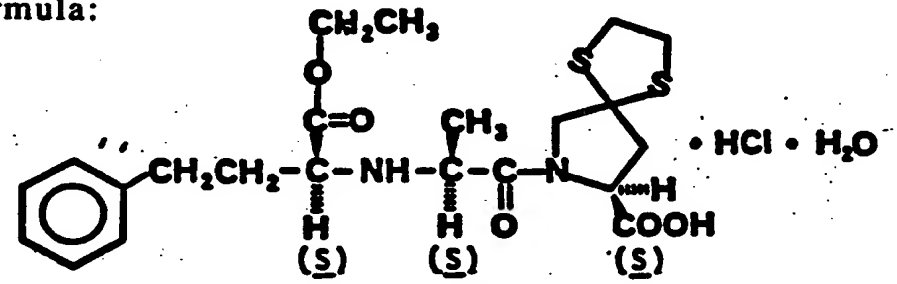
and the following generic name:

spirapril hydrochloride monohydrate; Schering reference Sch 33844

and the following registered tradename:

RENORMAX® (brand of spirapril hydrochloride monohydrate) tablets (Sandoz reference T1 211-950)

and is represented by the following structural formula:



7-[N-[1-(S)-Ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid Hydrochloride monohydrate is the active ingredient in the product RENORMAX® (brand of spirapril hydrochloride monohydrate) tablets as may be seen from Attachment No. 1 (Exhibit I) on which was submitted to the FDA with IND #23,278 for the approved product.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under Section 505(b) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S. Sec. 301 et seq. Section 505(b) provides for the submission and approval of new drug applications ("NDAs") for human drug products meeting the definition of "new drug" under Section 201(p) of the Act.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

RENORMAX® (brand of spirapril hydrochloride monohydrate) tablets was approved by the FDA for commercial marketing on December 29, 1994 (See Exhibit VIII)

(4) In the case of a (human) drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act or the Virus-Serum Toxin Act or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients) and the provision of law under which it was approved.

The active ingredient in the approved product, (brand of spirapril hydrochloride monohydrate) tablets, has the generic name of spirapril hydrochloride monohydrate and the chemical names listed in paragraph no. (1) hereinabove as well as in Attachment No. 1 (Exhibit I). The approved product RENORMAX (brand of spirapril hydrochloride monohydrate) tablets contains spirapril hydrochloride monohydrate as the sole active ingredient which active ingredient has not previously been approved for commercial marketing or use under the FFDCA. The FDA has approved RENORMAX (brand of spirapril hydrochloride monohydrate) tablets for treatment of hypertension. RENORMAX (brand of spirapril hydrochloride monohydrate) tablet NDA was approved by the FDA under Section 505(b) of the FFDCA (See Exhibit VIII).

(5) A statement that the application is being submitted within the sixty day period permitted for submission

pursuant to Sec. 1.720(f) and an identification of the date of the last day on which the application could be submitted:

The product was approved on December 29, 1994 and the last day within the sixty day period permitted for submission on an application for extension of the relevant U.S. Patent is February 27, 1995. This application is being timely filed before the February 27, 1995 deadline.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, and the date of issue:

United States Patent No. 4,470,972
Inventors: Elijah H. Gold, Bernard R. Neustadt and Elizabeth M. Smith
Date of Issue: September 11, 1984

(7) A copy of the patent for which an extension is being sought including the entire specification (including claims), and drawings:

A copy of the patent is attached as Exhibit II.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent:

No disclaimers or certificates of correction were filed for U.S. Patent No. 4,470,972.

A copy of the Maintenance Fee Receipt for the 8th year (dated April 8, 1992) is attached hereto as Exhibit X.

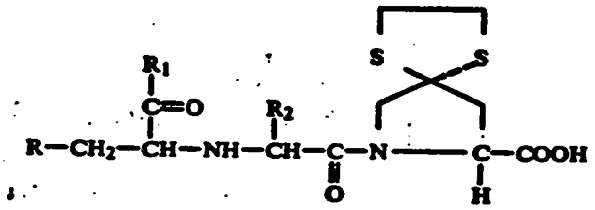
United States Patent No. 4,470,972 has not been re-examined and as such no re-examination certificate has been issued.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent

claim reads on the approved product or a method of using or manufacturing the approved product:

United States Patent No. 4,470,972 issued with 29 claims.

Claim 1 is directed to a compound represented by the formula



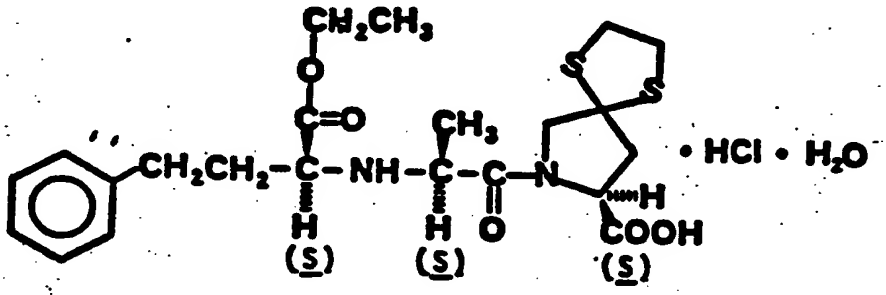
wherein:

R is a lower alkyl, benzyl, benzylthio, benzyloxy, phenylthio or phenoxy;

R_1 is hydroxy or lower alkoxy;

R_2 is hydrogen, lower alkyl or aminoloweralkyl; and the pharmaceutically acceptable salts thereof.

The structural formula for spirapril hydrochloride monohydrate is set forth on page 1 of Attachment No. 1 of Exhibit I herein above is



Thus, claim 1 covers spirapril hydrochloride monohydrate wherein R is benzyl, R_1 is lower alkoxy and R_2 is lower alkyl.

Claim 2 reads: A compound of claim 1 wherein R_2 is methyl.

Claim 2 covers spirapril hydrochloride monohydrate in that R_2 is a methyl which is a lower alkyl group.

Claim 3 reads: A compound of claim 2 wherein R_1 is lower alkoxy.

Claim 3 covers spirapril hydrochloride monohydrate in that R_1 is ethoxy which is a lower alkoxy group (and R_2 is methyl).

Claim 4 reads: A compound of claim 3 wherein R is benzyl.

Claim 4 covers spirapril hydrochloride monohydrate in that R is benzyl (and R_1 is ethoxy and R_2 is methyl).

Claim 5 reads: A compound of claim 4 wherein R_1 is ethoxy.

Claim 5 covers spirapril hydrochloride monohydrate in that R_1 is ethoxy (and R is benzyl and R_2 is methyl).

Claim 6 reads: A compound of claim 5 which is 7-[N-(1(S)-carboethoxy-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid hydrochloride.

Claim 6 specifically covers spirapril hydrochloride monohydrate (See chemical names in paragraph (1) hereinabove and Attachment No. 1 (Exhibit I).

Claim 24 reads: A compound of claim 1 wherein the pharmaceutically acceptable salt is an acid salt.

Claim 24 covers spirapril hydrochloride monohydrate in that claim 1 covers spirapril hydrochloride monohydrate and hydrogen chloride is an acid salt.

Claim 25 reads: A compound of claim 24 wherein the acid salt is hydrochloride or hemimaleate.

Claim 25 covers spirapril hydrochloride monohydrate for reasons stated in reference to claims 1 and 24.

Claim 26 reads: A pharmaceutical composition comprising an antihypertensive effective amount of a compound according to claim 1 together with a pharmaceutically acceptable carrier.

Claim 26 covers spirapril hydrochloride monohydrate tablets for reasons stated in reference to claim 1 and in that the oral tablet is a pharmaceutical composition and spirapril hydrochloride monohydrate was approved by the FDA for treatment of hypertension.

Claim 27 reads: A pharmaceutical composition comprising an antihypertensive effective amount of a compound according to claim 6 together with a pharmaceutically acceptable carrier.

Claim 27 covers spirapril hydrochloride monohydrate tablets for the reasons stated in reference to claims 6 and 26.

Claim 28 reads: A method of treating hypertension in mammals comprising administering to a mammal afflicted with hypertension an effective amount of a compound according to claim 1.

Claim 28 covers spirapril hydrochloride monohydrate tablets approved for treating hypertension in humans for the reasons stated herein above in reference to claims 1, 26, and 27.

Claim 29 reads: A method of treating hypertension in mammals comprising administering to a mammal afflicted with hypertension an effective amount of a compound according to claim 6.

Claim 29 covers spirapril hydrochloride monohydrate for treating hypertension in humans for reasons stated herein above in reference to claims 6 and 28.

The approved drug is disclosed in United States Patent No. 4,470,972 in Example 4 as 7-[N-1(S)-Ethoxycarbonyl-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azspiro[4.4]nonane-8(S)-carboxylic acid hydrochloride at col 7 lines 1-17 (and claim 6) and Example 9 at col 9 line 58 to col 10 line 24.

The approved indication for the approved drug is disclosed in United States Patent No. 4,470,972 at col 8, lines 48-60:

> "The compounds of this invention are useful in view of their pharmacological properties. In particular, they possess activity as antihypertensive agents as evidenced by their ability to reduce blood pressure in mammals in which the blood pressure has become abnormally elevated.
>
> The compounds of the present invention can be combined with pharmaceutical carriers and administered in a variety of well known pharmaceutical forms suitable for oral or parenteral administration to provide compositions useful in the treatment of cardiovascular disorders and particularly mammalian hypertension."

Thus, the approved drug for the approved indication (treatment of hypertension) is embraced by claims 1-6 and 24-29 of United States Patent No. 4,470,972.

(10) A statement beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. Sec. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a new drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued:

Schering Corporation ("Schering") of Kenilworth, New Jersey, is the assignee of record of United States Patent No. 4,470,972 by virtue of the Assignment dated December 3, 1982 by Elijah H. Gold, Bernard R. Neustadt and Elizabeth M. Smith of their interest in U.S. Patent No. 4,470,972 (Exhibit IX) recorded in the USPTO on January 28, 1983 at REEL: 4088, FRAME: 257.

In furtherance of the need for an approved NDA, Schering, on December 22, 1983 submitted to the FDA, a "Notice of Claimed Investigational Exemption for a New Drug" (hereinafter referred to as an "IND") under §505(i) of the FFDCA for the purpose of conducting clinical studies to support the approval of a subsequent NDA for Sch 33844 (spirapril hydrochloride monohydrate) oral capsules a non-sulfhydryl ACE inhibitor for treatment of hypertension. The Schering letter transmitting the IND to the FDA is attached as Exhibit III. By a letter dated January 11, 1984, the FDA acknowledged the date of receipt of the IND as December 23, 1983, assigned the IND number 23,278, and indicated that the IND study may be initiated 30 days after the date of receipt, i.e., on January 22, 1984. A copy of this FDA letter is attached as Exhibit IV. This establishes the beginning of the "regulatory review period" under 35 U.S.C. §156(g)(1) as January 22, 1984, the effective date of an Investigational exemption under §505(i).

Schering in a letter dated May 1, 1986 (copy attached as Exhibit V) advised the FDA that IND 23,278 had been transferred to Sandoz Pharmaceuticals Corporation ("Sandoz"). Sandoz in a letter dated May 29, 1986 (copy attached as Exhibit

VI) confirmed to the FDA that Sandoz had assumed responsibility for IND 23,278 for Sch 33,844 (spirapril hydrochloride monohydrate) oral and that Sandoz would be referring to Sch 33,844 as the Sandoz reference TI 211-950 capsules. Thereafter, the TI 211-950 capsule IND was amended by the filing of a TI 211-950 (spirapril hydrochloride) tablet formulation.

Sandoz submitted a NDA for TI 211-950 (spirapril hydrochloride) tablets, NDA No. 20-240 on December 30, 1991. A copy of this Sandoz letter transmitting the NDA is attached as Exhibit VII. By a letter dated January 13, 1992, the FDA acknowledged the date of receipt of NDA No. 20-240 for Spirapril Hydrochloride Monohydrate Tablets as December 31, 1991 and indicated the effective filing date would be February 28, 1992. A copy of this FDA letter is attached as Exhibit XI.

By a letter dated December 29, 1994 (copy attached as Exhibit VIII) the FDA advised Sandoz that the NDA No. 20-240 for use of RENORMAX® (spirapril hydrochloride monohydrate) tablets in the treatment of hypertension was approved effective on December 29, 1994.

Thus, for purposes of determining the "testing phase" of the "regulatory review period" under 35 U.S.C. §156(g)(1)(B)(i), the "testing phase" began on January 22, 1984, the date of the exemption under subsection (i) of §505 became effective and ended on December 30, 1991, the date the NDA No. 20-240 was initially submitted by Sandoz for spirapril hydrochloride tablets under §505(b) of the FFDCA. And, for purposes of determining the "approval phase of the "regulatory review period" under 35 U.S.C. §156(g)(1)(B)(ii) the "approval phase" began on December 31, 1991, the date the NDA 20-240 for spirapril hydrochloride tablets was initially submitted by Sandoz to the FDA and ended on December 29, 1994, the date on which the NDA No. 20-240 was approved by the FDA.

(11) A brief description beginning on a new page of the activities undertaken by Schering and Sandoz, the marketing applicants during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

During the applicable regulatory review period, Schering, and thereafter Sandoz the final marketing applicant, were actively involved in obtaining FDA approval for spirapril hydrochloride monohydrate tablets. As previously noted, Schering submitted an IND for spirapril hydrochloride monohydrate capsules on December 22, 1983 and in close consultation with the FDA conducted clinical trials in 1984 through May 1, 1986 under IND No. 23,278 at which date Schering transferred the responsibility to Sandoz for all aspects of progressing IND No. 23,278. On May 29, 1986, Sandoz confirmed to the FDA that it had assumed the responsibility for progressing IND No. 23,278 and agreed to continue to conduct clinical trials and to report any alarming reactions and to submit progress reports for spirapril hydrochloride monohydrate. Sandoz thereafter amended the IND by filing a spirapril hydrochloride monohydrate tablet formulation. On December 30, 1991, Sandoz submitted NDA No. 20-240 for TI 211-950 (spirapril hydrochloride monohydrate) tablets and in support of this NDA submitted both U.S. and European safety and efficacy trials as well as several supportive European study reports. During 1992 to 1994 Sandoz continued to interact with various FDA officials and answered numerous questions, generated requested data and supplied requested information regarding all clinical studies and data on spirapril hydrochloride monohydrate tablets submitted worldwide to obtain health approval. A brief description of the significant activities undertaken by Schering and Sandoz with respect to spirapril hydrochloride monohydrate capsules and tablets during the regulatory review period is set forth in Exhibit XIIa (IND) and Exhibit XIIb (NDA) and is illustrative of the activities involved.

(12) A statement that in the opinion of the applicant the patent is eligible for an extension and a statement as to the length of the extension claimed, including how the length of extension was determined:

(a) Statement of eligibility of the patent for extension under 35 U.S.C. §156(a):

Section 156(a) provides, in the relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended; (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) The term of United States Patent No. 4,470,972 currently expires on September 11, 2001. This application is, therefore, being submitted prior to the expiration of the term of United States Patent No. 4,470,972.

(2) The term of this patent has never been extended.

(3) This application is being submitted by the owner of record, Schering Corporation by virtue of the Assignment by Elijah H. Gold, Bernard R. Neustadt and Elizabeth M. Smith of their interests which was recorded in the USPTO on January 28, 1983, at Reel: 4008, Frame: 252 (copy attached as Exhibit IX). This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty-day period beginning on December 29, 1994, the date the product received permission for marketing under the FFDCA and ending on February 27, 1995 and contains the information required under 35 U.S.C. §156(d).

(4) As evidenced by the December 29, 1994 letter to Sandoz from the FDA (Exhibit VII), the product was subject to a regulatory review period under §505(b) of the FFDCA before its commercial marketing or use.

(5) Finally, RENORMAX® (brand of spirapril hydrochloride monohydrate) tablets were approved by the FDA

for treatment of hypertension. The permission for the commercial marketing of RENORMAX (brand of spirapril hydrochloride monohydrate) tablets after regulatory review under §505(b) is the first permitted commercial marketing of the active ingredient in RENORMAX (brand of spirapril hydrochloride monohydrate) tablets. This is confirmed by the absence of any approved new drug application for the active ingredient prior to December 29, 1994.

(b) Statement as to length of extension claimed:

The term of United States Patent No. 4,470,972 should be extended by two years (730 days). This extension was determined on the following basis. As set forth in 35 U.S.C. § 156(g)(1), the regulatory review period equals the length of time between the effective date of the initial IND No. 23,278 of January 22, 1984 and the initial submission of the NDA 20-240 on December 30, 1991, a period of 2899 days, plus the length of time between the initial submission of the NDA 20-240 (December 30, 1991) to NDA approval (December 29, 1994), a period of 1095 days. These two periods added together equal 3994 days.

Pursuant to 35 U.S.C. Sec. 156(c), the term of the patent eligible for extension shall be extended by the time equal to the regulatory review period which occurs after the date the patent is issued. In this case, Sec. 156(c) does apply in that the issue date of United States Patent No. 4,470,972 (September 11, 1984) is after the January 22, 1984 date on which the regulatory review period began. Thus, we subtract 233 days from 2899 day period to give a period of 2666 days.

The calculation made pursuant to Sec. 156(c)(2), requires the above period to be reduced by one-half of the 2666 day period; this calculation results in a value of 1333 days.

From the foregoing calculation, an extension of 2428 days, that is, almost 7 years thereby results. However, pursuant to 35 U.S.C. Sec. 156(g)(4)(c), the period of extension determined under any of the preceding paragraphs may not exceed two years (1) if the patent involved was issued before the date of enactment of this section; and (2) if an action described in subparagraph (b) was taken before the date of enactment of this section with respect to the approved product; and (3) if the commercial

marketing or use of the product has not been approved before such date.

As discussed below by the corresponding number, each of the elements of 35 U.S.C. Sec. 156(g)(4)(c) applies:

(1) The instant patent, United States Patent No. 4,470,972 was issued on September 11, 1984 which is a date before September 24, 1984, the date of enactment of 35 U.S.C. Sec. 156(g)(4)(C); (2) an IND for the drug was submitted on December 22, 1983 and having an effective date of January 22, 1984 which is a date before the date of enactment of the relevant section; and (3) the commercial marketing or use for the drug was approved on December 29, 1994 which is a date after the date of enactment of the relevant section.

Since the period of extension for the involved patent determined under 35 U.S.C. Sec. 156(c) is equal to the sum of 1333 days plus 1095 days or 2428 days, which is greater than 2 years (730 days), the term of the involved patent is eligible for a two year (730 day) extension under 35 U.S.C. Sec. 156(g)(4)(C).

Pursuant to Section 156(c)(3), if the period remaining in the term of the patent after the date of approval, that is, December 29, 1994 to September 11, 2001 (representing a period of 2194 days) when added to the period of extension determined under 35 U.S.C. Section 156(g)(4)(c) (that is a period of 730 days) exceeds 14 years (5,113 days), the period of extension must be reduced so that the total of both such periods does not exceed fourteen years. In this case, the total of both such periods is 2925 days which is less than 5,113 days, i.e. 14 years and accordingly 35 USC Sec. 156(c)(3) is not applicable.

Accordingly, the term of the patent is eligible for a two year (730 day) extension.

(13). Applicant acknowledges a duty to disclose to the ommissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determination to be made relative to the application for extension.

As stated in paragraph no. (9) hereinabove, claims 1, 2, 3, 4, 5, 6, 24, 25, 26, 27, 28 and 29 of the instant United States Patent No. 4,470,932 embrace the approved product, RENORMAX® (brand of spirapril hydrochloride monohydrate) tablets and the approved indication and usage of said approved product.

The term of United States Patent No. 4,470,972 has never been extended. A copy of this patent is attached as Exhibit II.

(14). Prescribed fees:

The Commissioner is authorized to charge our Deposit Account No. 19-0365 in the amount of $1,030.00 or any other fee necessary for this application to prevent it from becoming inadvertently abandoned.

(15). The name, address and telephone number of the person to whom inquiries and correspondence relating to this application for patent term extension are to be directed to:

Thomas D. Hoffman
Schering-Plough Corporation
Patent Department (K-6-1 - 1990)
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Tel. No. (908) 298-5037

(16). Certification that the enclosed duplicate copy of this application is a true copy of the original:

DECLARATION FOR EXTENSION OF UNITED STATES PATENT NO. 4,470,972

I, Thomas D. Hoffman, Registration No. 28,221, as duly appointed attorney for Applicant, Schering Corporation, the owner of record of United States Patent No. 4,470,972 (by virtue of the aforesaid Assignment Exhibit IX) which has applied for an extension of term of this patent, declare that I have reviewed and understand the contents of the attached application for extension of United States Patent No. 4,470,972; that I believe that the patent is subject to extension under 35 U.S.C. Sec. 156; that I believe that the length of extension claimed is fully justified under 35 U.S.C. Sec. 156, and that I believe that the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. Sec. 156. I certify that the duplicate copy of this application transmitted herewith is a true copy of the original application.

I hereby acknowledge that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of United States Patent No. 4,470,992.

Date: 02/21/95

Thomas D. Hoffman
Attorney for Assignee of Record
Reg. No. 28,221
Tel. No. (908) 298-5037

17. DECLARATION AND POWER OF ATTORNEY BY OWNER OF RECORD

As the below identified official of Schering Corporation, the owner of record of United States Patent No. 4,470,972, which has applied for an extension of term of this patent, I declare (1) that I have been authorized to practice before the United States Patent and Trademark Office and have authority from the owner of record to act on behalf of the owner of record in patent matters; (2) that I have reviewed and understand the contents of the attached application for extension of United States Patent No. 4,470,972; (3) that I believe that the patent is subject to extension under 35 U.S.C. Sec. 156 and 37 C.F.R. Sec. 1.710; (4) that I believe that the length of extension claimed is fully justified under 35 U.S.C. Sec. 156 and the applicable regulations; and (5) that I believe that the patent for which an extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. Sec. 156 and 37 C.F.R. Sec. 1.720.

I hereby acknowledge that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and United States Patent No. 4,470,972.

POWER OF ATTORNEY: I hereby appoint as United States attorneys and with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: Thomas D. Hoffman Registration No. 28,221; John J. Maitner, Registration

No. 25,636; Norman C. Dulak, Registration No. 31608; Edward H. Mazer, Registration No. 27,573; and Eric S. Dicker, Registration No. 31,699.

Send correspondence to:

Thomas D. Hoffman,
Schering-Plough Corporation
Patent Department K-6-1-1990
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530
Tel. No. (908) 298-5037

Date: February 21, 1995

By: James R Nelson
James R. Nelson
Vice President -
Schering Corporation
Reg. No. 27,929

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: United States Patent No. 4,470,972	:	
Inventors: Elijah H. Gold, Bernard R. Neustadt and Elizabeth M. Smith	:	Attn: Box Patent Ext.
Issue Date: September 11, 1984	:	

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

LETTER OF TRANSMITTAL OF APPLICATION FOR EXTENSION OF PATENT TERM

Sir:

Transmitted herewith for filing is an application for extension of term of U.S. Patent No. 4,470,972 and a duplicate of the papers thereof, certified as such.

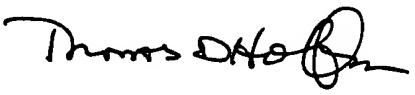
Also submitted herewith is an additional original declaration for extension of U.S. Patent No. 4,470,972. Therefore, the present application is complete and entitled to a filing date of February 22, 1995.

Pursuant to the provisions of 37 C.F.R. §1.785(c), the undersigned appointed attorney for Applicant, Schering Corporation ("Schering"), states that Sandoz Pharmaceuticals Corporation ("Sandoz") is the holder of the regulatory approval granted with respect to the regulatory review period for RENORMAX® (brand of spirapril hydrochloride monohydrate) oral tablets as evidenced by (1) the submission on December 22, 1983 by Schering of IND No. 23,278 [date of receipt of the IND by the Food and Drug Administration ("FDA") is December 23, 1983] for spirapril

hydrochloride monohydrate (Sch 33844) oral capsules, an angiotensin converting enzyme ("ACE") inhibitor, useful for treatment of hypertension (See attached Exhibits III and IV); (2) the letter dated May 1, 1986 from Schering to the FDA advising the FDA that responsibility for IND No. 23,278 has been transferred to Sandoz (Exhibit V); (3) the letter dated May 29, 1986 from Sandoz to the FDA confirming that Sandoz has assumed the responsibility for IND No. 23,278 (Exhibit VI); (4) the submission on December 30, 1991 by Sandoz of NDA No. 20-240 for spirapril hydrochloride monohydrate tablets; (Exhibit VII); and (5) the letter dated December 29, 1994 approving NDA No. 20-240 for RENORMAX® (brand of spirapril hydrochloride monohydrate) oral tablets as an ACE inhibitor indicated for treatment of hypertension (Exhibit VIII).

The Commissioner is hereby authorized to charge payment in the amount of $1,030.00 and of any additional fees associated with this communication or credit any overpayment to Deposit Account No. 19-0365. A duplicate copy of this sheet is enclosed.

Respectfully submitted,



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SCHERING-PLOUGH CORPORATION
Patent Department K-6-1-1990
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530

EXHIBIT I

1-1

Attachment No. 1

The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered.

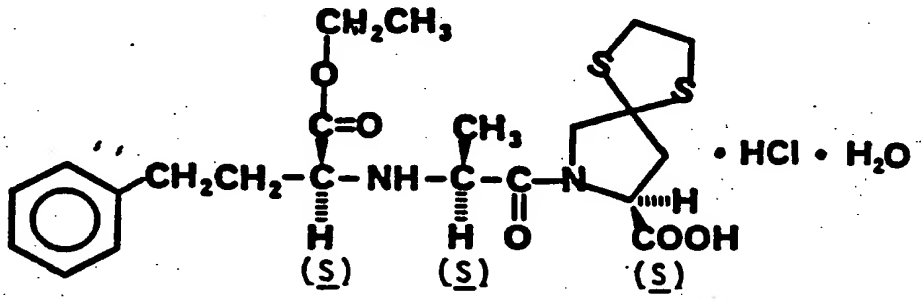
Descriptive Name of Drug Sch 33844 Hydrochloride Oral

New Drug Substance

Code Name: Sch 33844 Hydrochloride Monohydrate

Generic Name of Drug Substance: Not available

Structure:



Chemical Name: 7-[N-[1-(S)-Ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic Acid Hydrochloride Monohydrate

Empirical Formula: $C_{22}H_{30}N_2O_5S_2 \cdot HCl \cdot H_2O$

Molecular Weight: 521.1

Dosage Form: Capsules

Trade Name: Not available

Mode of Administration: Oral

Attachment No. 2

Complete list of components of the drug, including any reasonable alternates for inactive components.

SCH 33844 Hydrochloride Capsules, 12.5 mg, 25 mg and 50 mg

SCH 33844 Hydrochloride*

Lactose, Hydrous, USP

Silica Gel NF

Two-piece No. 0 maroon opaque hard gelatin capsules

*Charged as Sch 33844 Hydrochloride Monohydrate, Micronized

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21402

Attachment No. 3

Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

SCH 33844 Hydrochloride Capsules, 12.5 mg, 25 mg and 50 mg

Formula	mg/capsule*		
Active			
Sch 33844 Hydrochloride**	12.5	25	50
Excipients			
Lactose, Hydrous USP	335-500	320-490	300-460
Silica Gel NF	8-12	8-12	8-12
Approximate Capsule Fill Weight	350-530	350-530	350-530

*Filled into No. 0 maroon opaque, two-piece hard gelatin capsules.

**Charged as Sch 33844 Hydrochloride Monohydrate, Micronized. May include up to a 2% manufacturing overcharge.

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EXHIBIT II

United States Patent [19]

Gold et al.

[11] **Patent Number: 4,470,972**

[45] **Date of Patent: Sep. 11, 1984**

[54] **7-CARBOXYALKYLAMINOACYL-1,4-DITHIA-7-AZASPIRO[4.4]-NONANE-8-CARBOXYLIC ACIDS**

[75] **Inventors:** Elijah H. Gold; Bernard R. Neustadt, both of West Orange; Elizabeth M. Smith, Verona, all of N.J.

[73] **Assignee:** Schering Corporation, Kenilworth, N.J.

[21] **Appl. No.:** 446,929

[22] **Filed:** Dec. 6, 1982

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 258,484, Apr. 28, 1981, , which is a continuation-in-part of Ser. No. 201,649, Oct. 28, 1980, abandoned, which is a continuation-in-part of Ser. No. 199,886, Oct. 23, 1980, abandoned.

[51] **Int. Cl.**³ **A61K 37/00; A61K 31/40**

[52] **U.S. Cl.** **424/177**

[58] **Field of Search** 424/177, 274; 548/409

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,311,697	1/1982	Krapcho	548/409
4,325,945	4/1982	Natarajan et al.	548/409

Primary Examiner—Delbert R. Phillips

[57] **ABSTRACT**

This invention relates to 7-carboxyalkyl-aminoacyl-1,4-adithia-7-azaspiro[4.4]nonane-8-carboxylic acids. The compounds of the invention are useful in the treatment of cardiovascular disorders and especially as antihypertensive agents.

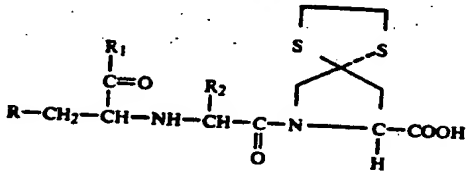
29 Claims, No Drawings

7-CARBOXYALKYLAMINOACYL-1,4-DITHIA-7-AZASPIRO[4.4]-NONANE-8-CARBOXYLIC ACIDS

This application is a continuation-in-part of U.S. Ser. No. 258,484, filed Apr. 28, 1981, which is a continuation-in-part of U.S. Ser. No. 201,649, filed Oct. 28, 1980, now abandoned, which is a continuation-in-part of U.S. Pat. No. 199,886, filed Oct. 23, 1980, now abandoned.

The present invention relates to 7-carboxyalkylaminoacyl-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acids. The compounds of the invention are useful in the treatment of cardiovascular disorders and especially as antihypertensive agents.

Compounds of the present invention are represented by the following formula



I

wherein:

R is lower alkyl, benzyl, benzylthio, benzyloxy, phenylthio or phenoxy;

R_1 is hydroxy or lower alkoxy;

R_2 is hydrogen, lower alkyl or amino lower alkyl;

and the pharmaceutically acceptable salts thereof.

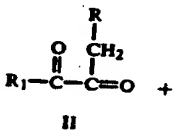
In the above description, lower alkyl refers to straight or branched chain alkyl groups having from 1 to 6 carbon atoms, e.g. methyl, ethyl, propyl, isopropyl, butyl, pentyl, 3-methylbutyl, and hexyl, lower alkoxy refers to alkoxy groups having from 1 to 6 carbon atoms, e.g. methoxy, ethoxy, and propoxy, and amino lower alkyl refers to groups having from 1 to 6 carbon atoms, e.g. aminomethyl, aminoethyl, 3-aminopropyl and 4-aminobutyl.

In preferred compounds of formula I, R_2 is hydrogen, methyl or aminobutyl. Also preferred are compounds of formula I wherein R_1 is lower alkoxy. A third preferred group contains compounds of formula I wherein R is benzyl. More preferred are compounds of formula I wherein R is benzyl, R_1 is lower alkoxy and R_2 is methyl. Most preferred are compounds wherein R is benzyl, R_1 is ethoxy and R_2 is methyl.

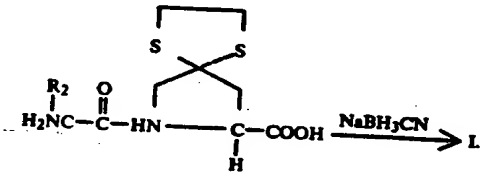
Preferred compounds of the invention are 7-[N-(1(S)-carboethoxy-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid, 7-[Nα-(1(S)-carboethoxy-3-phenylpropyl)-(S)-lysyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid and 7-[Nα-(1(S)-carboxy-3-phenylpropyl)-(S)-lysyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid.

The compounds of the present invention can be produced by various methods and subroutes, one of which is depicted in the following equations. Additional methods may be found in European Patent Application No. 50,800, filed Oct. 15, 1981 and published May 5, 1982. Reactive groups not involved in the condensations described below such as amino, carboxy, mercapto, etc., may be protected by methods standard in peptide chemistry prior to the coupling reactions and subsequently deprotected to obtain the desired products. For example, if R_1 is alkoxy or protected by a carboxy protecting group such as benzyloxy, it can be converted by well known methods such as hydrolysis or hydrogenation to I, wherein R_1 is hydroxy. Such reactions are demonstrated in the Examples.

Compounds of the present invention are prepared as follows:



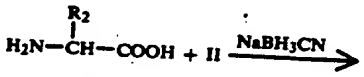
II



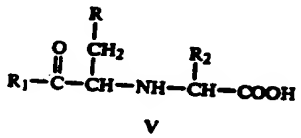
III

Keto acid (or ester) II is condensed with dipeptide III in aqueous solution, optimally near neutrality, or in a suitable organic solvent (for example, CH_3OH) in the presence of sodium cyanoborohydride to give I. Alternatively, the intermediate Schiff base, enamine, or aminol may be catalytically reduced to yield product I, for example, by hydrogen in the presence of palladium black. The ratio of diasteriomeric products formed may be altered by choice of catalyst.

Alternatively II can be condensed with an amino acid IV

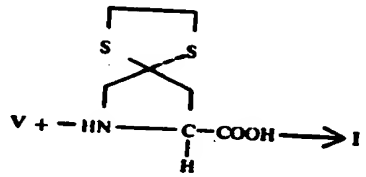


IV



V

under the same conditions to yield amino acid V. Subsequent coupling by known methods with amino acid derivative VI gives I.



VI

The known methods encompass reactive group protection during the coupling reaction, for example, by N-formyl, N-t-butoxycarbonyl and N-carbobenzyloxy groups followed by their removal to yield I. Furthermore, if desired, the carboxylic acid function in VI may be protected by removable ester groups such as benzyl, ethyl, t-butyl, and the like. Condensing agents in this synthetic route are typically those useful in peptide chemistry such as dicyclohexylcarbodiimide (DCC) or diphenylphosphoryl azide (DPPA) or V may be acti-

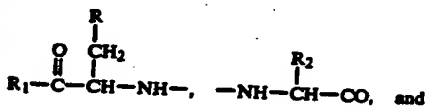
vated via the intermediacy of active esters such as that derived from N-hydroxysuccinimide, 1-hydroxybenzotriazole, and the like.

As desired, protecting groups may be removed by known methods.

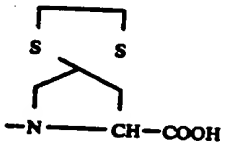
The starting materials which are required for the above processes herein described are known in the literature or can be made by known methods.

In the compounds of the formula I, the carbon atoms to which R—CH_2— and R_2— (where R_2 is not hydrogen) are attached and the carbon at the 8-position of the 1,4-dithia-7-azaspiro[4.4]nonane ring are asymmetric. The compounds accordingly exist in diastereoisomeric forms or in mixtures thereof. The above described synthesis can utilize racemates, enantiomers or diastereomers as starting materials. Enantiomeric intermediates may be obtained by resolution methods known in the art. When diastereomeric products result from the synthetic procedures, the diastereomeric products can be separated by conventional chromatographic or fractional crystallization methods.

In general, the amino acid part-structures, i.e.,



and



of formula I are preferred in the configuration analogous to that of natural L-amino acids. Usually, natural L-amino acids are assigned the S-configuration. A notable exception is the natural amino acid L-cysteine which is assigned the R-configuration.

The compounds of this invention form salts with various inorganic and organic acids and bases which salts are also within the scope of the invention. Such salts include ammonium salts, alkali metal salts, e.g. sodium and potassium salts, and alkaline earth metal salts, e.g. calcium and magnesium salts. Salts with organic and inorganic acids may be prepared, e.g., HCl, HBr, H_2SO_4, H_3PO_4, methanesulfonic acid, toluenesulfonic acid, maleic acid, fumaric acid and camphorsulfonic acid. The non-toxic physiologically acceptable salts are preferred, although other salts are also useful, e.g., in isolating or purifying the product. Especially preferred acid salts are the hydrochloride and the hemimaleate.

The salts may be formed by conventional means, as by reacting the free acid or base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed in vacuo, by freeze-drying, or by exchanging the cations of an existing salt for another cation on a suitable ion exchange resin.

The following examples illustrate the preparation of the compounds of the present invention. The diastereomers prepared as set forth below may be isolated by column chromatography or by fractional crystallation.

EXAMPLE 1

7-[N-(1-Carboethoxy-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid

A. Dissolve 7.0 g of 1-benzyloxycarbonyl-4-keto-(S)-proline methyl ester in 75 ml of glacial acetic acid. Add 0.7 g of p-toluenesulfonic acid and 2.8 g of 1,2-ethanedithiol and heat under reflux with stirring for eighteen hours. Add the reaction mixture to saturated sodium bicarbonate solution and extract with ethyl acetate. Dry the organic layer over magnesium sulfate and concentrate it. Place the residue on a column of silica gel (300 g, 60–200 mesh) and elute with hexane:ethyl acetate (1:1) to give 7-benzyloxycarbonyl-1,4-dithia-7-azaspiro-[4.4]nonane-8(S)-carboxylic acid methylester, a yellow oil having $[\alpha]_D^{26} - 12.6°$ (dioxane).

B. Dissolve 3.0 g of 7-benzyloxycarbonyl-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid methyl ester (3.0 g) in 20 ml of 20% hydrobromic acid in glacial acetic acid and stir the mixture at room temperature for two hours. Add the mixture dropwise to diethyl ether at 0°–5° to give 1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid methyl ester hydrobromide, a brown solid m.g. 156°–158°.

C. Dissolve the 1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid methyl ester hydrobromide from paragraph B in 0.1 N NaOH and extract with ethyl acetate. Dry the organic layer over magnesium sulfate and concentrate in vacuo to give 1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid methyl ester (1.35 g). Dissolve the latter in 100 ml of ethyl acetate and treat with 2.07 g of N-benzyloxycarbonyl-(S)-alanine, N-hydroxysuccinimide ester. Stir the reaction mixture at room temperature for eighteen hours and concentrate in vacuo. Place the residue on a column of silica gel (300 g, 60–200 mesh) and elute with hexane:ethyl acetate 4:1 to obtain 7-[N-benzyloxycarbonyl-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid, methyl ester, a yellow oil $[\alpha]_D^{26} = -14.8°$ (ethanol).

D. Dissolve 1.05 g of 7-[N-benzyloxycarbonyl(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid, methyl ester in 100 ml of methanol. Add 10 ml of 2.5 N sodium hydroxide and stir the mixture at room temperature for sixteen hours. Concentrate the mixture under nitrogen, dissolve the oil in 0.1 N sodium hydroxide and dilute with ice water. Adjust to pH2 with concentrated hydrochloric acid, then extract with ethyl acetate. Dry the organic phase over magnesium sulfate and concentrate it. Place the residue on a column of silica gel (100 g, 60–200 mesh) and elute with chloroform:glacial acetic acid 19:1 to obtain 7-[N-benzyloxycarbonyl-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid, $[\alpha]_D^{26} = -15.8°$ (ethanol).

E. Dissolve 1.4 g of 7-[N-benzyloxycarbonyl-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid in 20 ml of 20% hydrobromic acid in glacial acetic acid and stir the mixture at room temperature for two hours. Add the mixture dropwise to diethyl ether at 0°–5° C. to give 7-[(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid hydrobromide which is used immediately in the process described in paragraph F below.

F. Dissolve the 7-[(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid hydrobromide (prepared in paragraph E next above) in 100 ml of absolute methanol. Add 0.5 g of 2-oxo-4-phenylbutyric acid, ethyl ester and 10 ml of 3A molecular sieve pellets and

stir the mixture at room temperature for eighteen hours. Filter the reaction mixture and treat the filtrate with 0.30 g of sodium cyanoborohydride at room temperature for two hours. Concentrate the mixture under nitrogen and dilute the oil with 5% hydrochloric acid to pH 2 to 4 and stir at room temperature for one hour. Adjust the pH of the solution to pH 8 with 2.5 N sodium hydroxide solution and absorb the solution in 150 ml of XAD-2 resin. Elute the resin with 800 ml of water and then with 800 ml of methanol. Concentrate the methanol solution, place the residue on a column of silca gel (100 g, 60–200 mesh) and elute with chloroform:isopropanol:7% ammonium hydroxide 1:1:1 (organic layer) to obtain 7-[N-(1-carboethoxy-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid, a white solid, m.p. 56°–60° C., $[\alpha]_D^{26}$ −25.5° (ethanol).

EXAMPLE 2

7-[N-(1-Carboxy-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid

Hydrolyze 0.18 of the product of Example 1 in 20 ml of methanol with 1.3 ml of 2.5 N sodium hydroxide for 20 hours at room temperature. Concentrate the reaction mixture in vacuo at room temperature. Dissolve the resultant residue in water and place on Bio Rad AG-50W-X2 (100–200 mesh) resin in the hydrogen form. Elute with water (300 ml), then with 2% pyridine in water. Concentrate the desired eluant fractions to obtain the title compound.

EXAMPLE 3

7-[N-(1(S)-Carboethoxy-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid

A. Dissolve 1-benzyloxycarbonyl-4-keto-(S)-proline (15.7 g, 60 mmol) in acetic acid (45 ml) and ethyl acetate (45 ml), add 1,2-ethanedithiol (6.2 g, 66 mmol) and stir under nitrogen. Add boron trifluoride etherate (redistilled) and stir 4 hours. Pour the reaction mixture into a mixture of water (175 ml) ethyl acetate (120 ml) and ether (60 ml). Wash the organic layer with water (2×175 ml) then extract twice with 1.0 N sodium bicarbonate (150 ml, then 50 ml). Acidify the aqueous layer to pH 1 with concentrated hydrochloric acid, extract twice with ether (150 ml, then 50 ml). Wash the organic layer with brine, dry over anhydrous magnesium sulfate and concentrate in vacuo to obtain crude 7-benzyloxycarbonyl-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid as an oil (16.1 g).

B. Dissolve the product of Step A in acetic acid (30 ml) by stirring under nitrogen. Add 23% hydrobromic acid in acetic acid (50 ml), stir 3 hours and dilute over 5 minutes with ether (320 ml). Filter the solid, wash twice with ether (2×150 ml) and air dry to obtain a purple powder.

Dissolve the crude product in boiling ethanol (120 ml), add Darco grade 6–60 (6 g), and filter hot, washing with 2×10 ml hot ethanol. Dilute the filtrate with ether (90 ml) and allow to stand one hour. Filter the resulting precipitate, wash with ether (2×50 ml), and air dry to give 1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid hydrobromide as beige crystals.

(1)a. To a 5 L flask equipped with a magnetic stirrer, dropping funnel and nitrogen inlet tube, add a solution of 190 g (0.92 mole) of S-alanine benzyl ester benzenesulfonate and 258 g (0.734 mole) of 2-oxo-4-phenylbutanoate in 1.4 L of ethanol. Stir for 2 hours under nitrogen. Add a solution of 17.7 g (0.282 mole) of sodium cyanoborohydride in 550 mL of ethanol, with stirring, over 90 minutes. Stir the solution overnight and concentrate to dryness in vacuo at room temperature. Partition the residue between 500 mL of H_2O and 2 L of ether. Dry the ether layer over $MgSO_4$ and filter. Add 1.3 M ethereal HCl to pH 4. Remove the ether and excess HCl in vacuo at room temperature. Slurry the residue in 250 mL of ether and dilute with 750 mL of hexane. Decant the supernatent from the resulting precipitate and wash with two 300 mL portions of ether. Triturate the residue with 300 mL of ether and filter under N_2 to give 134 g of a white solid. Slurry the solid in ether and make basic with saturated aqueous $NaHCO_3$. Dry the organic layer over $MgSO_4$, filter and concentrate in vacuo at room temperature to give 135 g of N-(1-carboethoxy-3-phenylpropyl)-(S)-alanine benzyl ester as an amber oil.

Dissolve 135 g of the resultant amber oil in 510 ml of ethyl acetate and add a hot solution of 40.5 g maleic acid in 895 ml of ethyl acetate. Cool to room temperature, filter the resulting precipitate, and recrystallize the precipitate from ethyl acetate to give N-(1(S)-carboethoxy-3-phenylpropyl)-(S)-alanine benzyl ester hemimaleate as a white solid, m.p. 127°–128° C., $[\alpha]_D^{26}$=0° (H_2O).

Slurry 7.0 g (0.015 mole) of the above product in ethyl acetate and adjust to pH 8 with saturated aqueous sodium bicarbonate. Wash the organic layer with saturated aqueous sodium chloride solution, dry over magnesium sulfate, filter, and concentrate in vacuo at room temperature to a colorless oil. Dissolve the resultant oil in 100 ml ethanol containing 0.7 g of 10% Pd/C and hydrogenate at 60 psi at room temperature for 2 hours. Filter and evaporate the solvent under vacuum at room temperature to obtain 4.0 g of N-(1(S)-carboethoxy-3-phenylpropyl)-(S)-alanine as a white solid, m.p. 147°–148° C., $[\alpha]_D^{26}$+24.8° (methanol).

b. To a solution of the product of Step (1)a (8.93 g, 32 mmol) and N-hydroxysuccinimide (4.42 g, 38.4 mmol) in dry dimethylformamide (64 ml), add 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (7.3 g, 38.4 mmol) and stir for 12 hours. Pour the reaction mixture into ethyl acetate (320 ml), wash with water (100 ml), brine (100 ml), and dry the organic layer over anhydrous magnesium sulfate. Concentrate in vacuo to obtain N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-alanine succinimidyl ester as an oil.

(2) Dissolve the product of Step (1)b and 1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid hydrobromide (Step B) (9.16 g, 32 mmol) in dimethylformamide (155 ml) and cool to 0°–5° C. Add triethylamine (8.9 ml, 64 mmol) dropwise over 5 minutes, and rinse the funnel with dimethylformamide (5 ml). Stir at room temperature for 16 hours, concentrate in vacuo to 50 ml and dilute with water (150 ml). Adjust the solution to pH 4.0 with 1 N hydrochloric acid. Extract the resultant brown gum with ethyl acetate (4×100 ml), combine the extracts, wash with water (20 ml) then brine (20 ml) and dry the organic phase over anhydrous magnesium sulfate. Evaporate the solvent in vacuo to obtain the title compound as a brown oil.

To purify, dissolve the crude product (3.3 g) in methanol (10 ml), place on Sephadex LH-20 (2.5×55 cm column) and elute with methanol. Combine the desired fractions and evaporate the solvent in vacuo to give the title compound as a solid white foam. Analytically pure material has an $[\alpha]_D^{26}$=−29.5° (ethanol).

EXAMPLE 4

7-[N-(1(S)-Ethoxycarbonyl-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid hydrochloride

Dissolve the crude product of Example 3, Step C (27 g, 5.8 mmol) in acetonitrile (18 ml), add concentrated hydrochloric acid (0.5 ml, 6 mmol) and seed. After crystallization starts, refrigerate for 10 hours. Collect the crystals, wash with cold acetonitrile, then ether, and let dry to give crystals, m.p. 176°–178° C. (dec.).

To recrystallize the above product, dissolve the crystals (0.5 g) in hot methanol (1 ml), dilute with acetonitrile (5 ml) and seed. Refrigerate for 10 hours, collect the crystals and let dry to obtain the title compound, m.p. 176°–178° C., $[\alpha]_D^{26} = -11.2°$ (ethanol) (analytically pure material).

EXAMPLE 5

7-[N-(1(S)-Ethoxycarbonyl-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid hemimaleate

Dissolve the crude product of Example 3, Step C (2.9 g, 5.2 mmol) and maleic acid (0.7 g, 60 mmol) in hot acetonitrile (18 ml) and refrigerate for 10 hours. Collect the crystals, wash with cold acetonitrile and let dry to obtain the title compound as tan crystals (1.6 g). Analytically pure material has m.p. 124°–126° C., $[\alpha]_D^{26} = -14.3°$ (ethanol).

EXAMPLE 6

7-[N-(1(S)-Carboxy-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid

As described in Example 2, hydrolyze the product of Example 3 (0.3 g) in methanol (30 ml) with 2.5 N sodium hydroxide (2.0 ml) to give the title compound, m.p. 115°–117° C., $[\alpha]_D^{26} = -2.4°$ (H_2O); $+1.9°$ (ethanol).

EXAMPLE 7

7-[N-(1-Carboethoxy-3-phenylpropyl)glycyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid

A. As described in Example 1, react 1-benzyloxycarbonyl-4-keto-(S)-proline, ethyl ester (prepared from the acid by esterification in ethanol) with 1,2-ethane dithiol to obtain 7-benzyloxycarbonyl-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid, ethyl ester, a yellow oil $[\alpha]_D^{26} - 21.0°$ (ethanol).

B. Convert 2.22 g of 7-benzyloxycarbonyl-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid, ethyl ester (prepared as described in paragraph A) to 1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid, ethyl ester as described in Example 1 and couple this compound with 1.5 g of N-benzyloxycarbonylglycine, N-hydroxysuccinimide ester as described in Example 2 to yield 7-(N-benzyloxycarbonylglycyl)-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid, ethyl ester, a yellow oil $[\alpha]_D^{24} - 15.9°$. (ethanol).

C. Hydrolyze 1.43 g of 7-(N-benzyloxycarbonylglycyl)-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid, ethyl ester (prepared as described in paragraph B next above) with sodium hydroxide as described in Example 1D to obtain 7-(N-benzyloxycarbonylglycyl)-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid, a colorless oil, $[\alpha]_D^{26} - 7.9°$ (ethanol).

D. Treat 0.95 of the acid obtained in the process described in paragraph C next above with 20% hydrobromic acid in glacial acetic acid as described in Example 1E to obtain 7-glycyl-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid, hydrobromide, $[\alpha]_D^{26} - 18.7°$ (ethanol).

E. As described in Example 1F, couple 0.76 g of 7-glycyl-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid, hydrobromide (prepared as described in paragraph D next above) with 0.50 g of 2-oxo-4-phenylbutyric acid, ethyl ester to obtain 7-[N-(1-carboethoxy-3-phenylpropyl)glycyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid $[\alpha]_D^{26} - 39.0°$ (ethanol).

EXAMPLE 8

7-[N-(1-Carboxy-3-phenylpropyl)glycyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid

As described in Example 2, hydrolyze 7-[N-(1-carboethoxy-3-phenylpropyl)glycyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid (prepared as described in Example 2) with sodium hydroxide to give the title compound.

In a similar manner, using suitable reagents, prepare the following compounds:

7-[N-(1(S)-carbomethoxy-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid;

7-[N-(1(R)-carboethoxy-2-benzylthioethyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid;

7-[N-(1(S)-carboethoxy-2-phenoxyethyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid;

7-[Nα-(1(S)-carboethoxy-3-phenylpropyl)-(S)-lysyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid;

7-[Nα-(1(S)-carboxy-3-phenylpropyl)-(S)-lysyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid;

7-[N-(1(R)-carboethoxy-2-phenylthioethyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid; and

7-[N-(1(S)-carboethoxy-2-benzyloxyethyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid;

7-[N-(1(S)-carboethoxypentyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid;

7-[N-(1(S)-carboethoxybutyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid; and

7-[N-(1(S)-carboethoxyhexyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid.

The compounds of this invention are useful in view of their pharmacological properties. In particular, they possess activity as antihypertensive agents as evidenced by their ability to reduce blood pressure in mammals in which the blood pressure has become abnormally elevated.

The compounds of the present invention can be combined with pharmaceutical carriers and administered in a variety of well known pharmaceutical forms suitable for oral or parenteral administration to provide compositions useful in the treatment of cardiovascular disorders and particularly mammalian hypertension.

The effective daily antihypertensive dose (ED_{50}) of the compounds of this invention will typically be in the range of about 0.1 to about 10 mg/kg, of mammalian weight, administered in single or divided doses. The exact dose to be administered is dependent upon where the particular compound lies within the above quoted range, as well as upon the age, weight and condition of the individual.

Generally, in treating humans having hypertension, the compounds of this invention may be administered to patients in need of such treatment in a dose range of 5 to 150 mg per patient generally given twice daily, thus giving a total daily dose of from 10 to 300 mg per day. Also, the compounds of this invention may be given in combination with diuretics or other antihypertensives. Typically, these are combinations whose individual per day dosages range from one-fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they are given singly. Examples of such diuretics or other antihypertensives are hydrochlorothiazide, chlorothiazide, ethacrynic acid, amiloride, furosemide, propranolol, timolol and methyldopa.

The antihypertensive compositions containing the compounds of this invention will preferably contain from about 5 to about 250 mg of the active compound per dosage unit.

Since the compounds of the present invention are believed to act as angiotensin converting enzyme inhibitors, it is also contemplated that they may be used in treating other cardiovascular disorders, for example congestive heart failure, in the same manner as other ACE inhibitors such as captopril and MK-421 may be used.

The compositions of the present invention are most preferably administered orally. Typical formulations for oral administration are those such as tablets, capsules, syrups, elixirs or suspensions. Typical injectable formulations include solutions and suspensions.

Typical acceptable pharmaceutical carriers for use in the formulations described above are exemplified by: sugars such as lactose, sucrose, mannitol and sorbitol; starches such as corn starch, tapioca starch and potato starch; cellulose and derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; calcium phosphates such as dicalcium phosphate and tri-calcium phosphate; sodium sulfate; calcium sulfate, polyvinylpyrrolidone, polyvinyl alcohol; stearate acid; alkaline earth metal stearates such as magnesium stearate and calcium stearate, stearate acid vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil and corn oil; non-ionic, cationic and anionic surfactants; ethylene gylcol polymers; beta-cyclodextrin; fatty alcohols and hydrolyzed cereal solids; as well as other non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, antioxidants, lubricants, flavoring agents, and the like commonly used in pharmaceutical formulations.

The following example describes in detail a composition that is illustrative of the present invention. It will be apparent to those skilled in the art that many modifications, both of materials and methods, may be practiced without departing from the purpose and intent of this disclosure.

In the following example, the active ingredient is 7-[N-(1(S)-carboethoxy-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid hydrochloride, though any of the compounds of the invention may be similarly formulated.

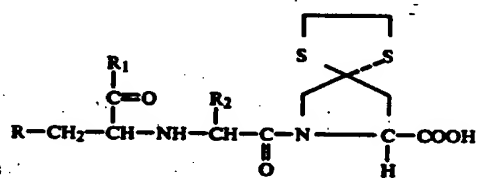
EXAMPLE 9

Tablet	Amount (mg)
Active Ingredient	75.0
Lactose	80.5
Corn Starch	6.0
Water (per thousand tablets)	60 ml (evaporates)
Corn starch	37.5
Magnesium Stearate	1.0
	200.0

Blend the active ingredient with the lactose until uniform. Blend the smaller quantity of corn starch with the water and add the resulting corn starch paste, then mix until a uniform wet mass is formed. Add the remaining corn starch to the remaining wet mass and mix until uniform granules are obtained. Screen the granules through a suitable milling machine, using a ¾ inch stainless steel screen. Dry the milled granules in a suitable drying oven until the desired moisture content is obtained. Mill the dried granules through a suitable milling machine using a 16 mesh stainless steel screen. Blend in the magnesium stearate and compress the resulting mixture into tablets of desired shape, thickness, hardness and disintegration.

We claim:

1. A compound represented by the formula



wherein:

R is a lower alkyl, benzyl, benzylthio, benzyloxy, phenylthio, or phenoxy;

R_1 is hydroxy or lower alkoxy;

R_2 is hydrogen, lower alkyl or aminoloweralkyl;

and the pharmaceutically acceptable salts thereof.

2. A compound of claim 1 wherein R_2 is methyl.

3. A compound of claim 2 wherein R_1 is lower alkoxy.

4. A compound of claim 3 wherein R is benzyl.

5. A compound of claim 4 wherein R_1 is ethoxy.

6. A compound of claim 5 which is 7-[N-(1(S)-carboethoxy-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]-nonane-8(S)-carboxylic acid hydrochloride.

7. A compound of claim 2 which is 7-[N-(1(S)-carboxy-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]-nonane-8(S)-carboxylic acid hydrochloride.

8. A compound of claim 2 which is 7-[N-(1(S)-carboxy-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]-nonane-8(S)-carboxylic acid.

9. A compound of claim 5 which is 7-[N-(1(S)-carboethoxy-3-phenylpropyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]-nonane-8(S)-carboxylic acid hemimaleate.

10. A compound of claim 1 wherein R_2 is hydrogen.

11. A compound of claim 1 wherein R_2 is aminobutyl.

12. A compound of claim 11 which is 7-[Nα-(1(S)-carboethoxy-3-phenylpropyl)-(S)-lysyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid dihydrochloride.

13. A compound of claim 11 which is 7-[Nα-(1(S)-carboethoxy-3-phenylpropyl)-(S)-lysyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid.

14. A compound of claim 11 which is 7-[Nα-(1(S)-carboxy-3-phenylpropyl)-(S)-lysyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid dihydrochloride.

15. A compound of claim 11 which is 7-[Nα-(1(S)-carboxy-3-phenylpropyl)-(S)-lysyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid.

16. A compound of claim 1 wherein R is benzylthio.

17. A compound of claim 1 wherein R is benzyloxy.

18. A compound of claim 1 wherein R is phenylthio.

19. A compound of claim 1 wherein R is phenyloxy.

20. A compound of claim 1 wherein R is lower alkyl.

21. A compound of claim 20 which is 7-[N-(1(S)-carboethoxypentyl)-(S)-alanyl]-1,4-dithia-7-azaspiro [4.4]-nonane-8(S)-carboxylic acid hydrochloride.

22. A compound of claim 20 which is 7-[N-(1(S)-carboethoxybutyl)-(S)-alanyl]-1,4-dithia-7-azaspiro[4.4]-nonane-8(S)-carboxylic acid hydrochloride.

23. A compound of claim 20 which is 7-[N-(1(S)-carboethoxyhexyl)-(S)-alanyl]-1,4-dithia-7-azaspiro [4.4]-nonane-8(S)-carboxylic acid hydrochloride.

24. A compound of claim 1 wherein the pharmaceutically acceptable salts is an acid salt.

25. A compound of claim 24 wherein the acid salt is hydrochloride or hemimaleate.

26. A pharmaceutical composition comprising an antihypertensive effective amount of a compound according to claim 1 together with a pharmaceutically acceptable carrier.

27. A pharmaceutical composition comprising an antihypertensive effective amount of a compound according to claim 6 together with a pharmaceutically acceptable carrier.

28. A method of treating hypertension in mammals comprising administering to a mammal afflicted with hypertension an effective amount of a compound according to claim 1.

29. A method of treating hypertension in mammals comprising administering to a mammal afflicted with hypertension an effective amount of a compound according to claim 6.

* * * * *

EXHIBIT III

SCHERING CORPORATION

CALLOPING HILL ROAD KENILWORTH, N. J. 07033

CABLES: SCHERING KENILWORTH
TELEX: 138316
138280
TELEPHONE: (201) 558-4000

December 22, 1983

Raymond J. Lipicky, M.D., Acting Director
Division of Cardio-Renal Drug Products
National Center for Drugs and Biologics
HFN 110, Room 16B-30
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: Sch-33844 Hydrochloride Oral

Dear Doctor Lipicky:

Submitted herewith, in triplicate, is a "Notice of Claimed Investigational Exemption for a New Drug" for Sch-33844 Hydrochloride Oral, a non-sulfhydryl angiotensin converting enzyme inhibitor.

Dr. Nadim Kassem, whose curriculum vitae appears on pages 9-6 to 9-7, will be the project physician for the subject IND.

Sincerely,

Nelson H. Schimmel, M.D.
Vice President
Regulatory Affairs

JM/ap

EXHIBIT IV

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 24 1984

NELSON H. SCHIMMEL M.D.

IND 23,278

JAN 11 1984

Schering Corporation
2000, Galloping Hill Road
Kenilworth, NJ
07033

Dear Sir/Madam: Dr. Schimmel

We are pleased to acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 23,278

Sponsor: Schering Corporation

Name of Drug: SCH-23844 hydrochloride oral

Date of Submission: December 22, 1983

Date of Receipt: December 23, 1983

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This responsibility includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

FORM FDA 3228a (6/82)

IND 23,278

JAN 24 1994

NELSON H. SCHIMMEL M.D. Page 2

As Sponsor of the clinical study proposed in this IND, you are now free to obtain supplies of the investigational drug.

The 30-day restriction does not apply if the IND number was assigned for the emergency use of the drug in one patient only.

Should you have any questions concerning this IND, please call:

Ms Jacqueline Knight
Consumer Safety Officer
(301) 443–4730

Please forward all future communications concerning this IND in TRIPLICATE IDENTIFIED with this IND NUMBER and addressed as follows:

Food and Drug Administration
Bureau of Drugs, HFD-110
Attention: DOCUMENT CONTROL ROOM # 16B-30
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

Natalia A. Morgenstern
Supervisory Consumer Safety Officer
Division of Cardio-Renal
Drug Products
Bureau of Drugs

CC:
Orig. File - pink
Division File - yellow
Division CSO - blue

ACKNOWLEDGEMENT

FORM FDA 3228b (6/82)

U.S. GOVERNMENT PRINTING OFFICE 1993-375-296

EXHIBIT V

RAYMOND M. GAST

MAY 2 1986

SCHERING CORPORATION

GALLOPING HILL ROAD KENILWORTH, N.J. 07033

CABLES: SCHERING KENILWORTH
TELEX: 138316
136280
TELEPHONE: (201) 558-4000

May 1, 1986

Raymond J. Lipicky, M.D., Acting Director
Division of Cardio-Renal Drug Products
Center for Drugs and Biologics (HFN 110)
Document Control Room 16B30
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: IND 23,278, Sch 33844 Hydrochloride Oral

Dear Dr. Lipicky:

This is to advise you that the above referenced IND has been transferred to Sandoz, Inc.

They will assume responsibility for all progress reporting and requirements coincident with the IND regulations. Dr. Peter Eden is the responsible person at Sandoz.

Sincerely,

Alexander R. Giaquinto, Ph.D.
Vice President
Regulatory Affairs

cc: Mr. Marcel Hugener,
Assistant Vice President
Sandoz, Ltd.

Dr. Peter Eden,
Director, Project Coordination
Sandoz, Inc.

bcc: Dr. Gonasun, Dr. Miller

EXHIBIT VI

SANDOZ RESEARCH INSTITUTE
SANDOZ, INC.

DRUG REGISTRATION &
REGULATORY AFFAIRS

EAST HANOVER, N.J. 07936

TELEPHONES
201 - 386 - 7500
212 - 349 - 1212
TELEX: 13 - 8352

May 29, 1986

Raymond Lipicky, M.D.
Acting Director, Division of Cardio-
Renal Drug Products/HFN-110
Office of Drug Research and Review
Attn: Document Control Room
16B-30
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

IND No. 23,278
Sch-33844 Hydrochloride
Oral
Transfer of IND
Sponsorship

Dear Dr. Lipicky:

Please refer to the Original Notice of Claimed Investigational Exemption for a New Drug for Sch-33844 Hydrochloride Oral, submitted on ~~November~~ December 22, 1983 by Schering Corporation.

On May 1, 1986, Alexander R. Guaguinto, Ph.D., Regulatory Affairs, Schering Corporation, notified you by letter that Sandoz Pharmaceuticals Corporation would be assuming the responsibility for this compound.

This letter will serve as confirmation that Sandoz Pharmaceuticals Corporation has assumed the responsibility for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations for this compound. This responsibility includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

Please note that in the future Sandoz will be referring to this compound as TI 211-950 Capsules.

Sincerely,

HM Ries for

C. Edward Eden, Ph.D.
Director, Project
Administration

/bmr
Submitted in triplicate
bcc: Dr. Gonasun, Dr. Miller

EXHIBIT VII

SANDOZ PHARMACEUTICALS CORPORATION
59 ROUTE 10, EAST HANOVER, NEW JERSEY 07936-1080

SANDOZ

SANDOZ RESEARCH INSTITUTE

DRUG REGISTRATION & REGULATORY AFFAIRS

TEL 201 503 7500
FAX 201 503 6325

December 30, 1991

Food and Drug Administration
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

NDA No. 20-240
TI 211-950 (spirapril hydrochloride) Tablets

Original New Drug Application

Gentlemen:

In accordance with 21 CFR 314.50, Sandoz Pharmaceuticals Corporation herewith submits an original new drug application for TI 211-950 (spirapril hydrochloride) Tablets.

TI 211-950 (spirapril hydrochloride), an angiotensin converting enzyme (ACE) inhibitor, is indicated for the treatment of hypertension.

In the United States, TI 211-950 (spirapril hydrochloride) Capsules/Tablets was studied under IND No. 23,278, which resides in the Division of Cardio-Renal Drug Products/HFD-110. This IND was initially held by Schering Corporation, Kenilworth, N.J., and was transferred to Sandoz Pharmaceuticals Corporation on May 1, 1986, pursuant to a licensing agreement.

In support of this application, we submit both U.S. and foreign safety/efficacy trials. Five (5) pivotal randomized, double-blind, placebo-controlled, multicenter trials were completed in the United States (Study Nos. 2, B301, B313, B314, and B321), as were three (3) active controlled studies (Study Nos. B316, B317, and S85-006), and five (5) uncontrolled open-label long-term studies (Study Nos. 2, B301, B314, B316, and B321). In multiple dose U.S. studies in hypertension, 1342 subjects received TI 211-950 alone or in combination with other agents, with 1200 of these subjects receiving TI 211-950 in controlled comparisons with placebo or active agents. In addition, over 400 subjects received TI 211-950 in U.S. open-label long-term hypertension studies.

In addition to the U.S. data, several supportive European study reports are included in this application. These include placebo-controlled, active controlled, and uncontrolled studies. The European studies provide additional corroborating information on the efficacy and safety of TI 211-950 in the treatment of hypertension. However, these studies were not conducted under U.S. IND No. 23,278, and were therefore not monitored or audited by Sandoz U.S. personnel. In the European studies, 1851 subjects received TI 211-950, of which 1614 subjects were hypertensive.

Sandoz Pharmaceuticals Corporation considers the information contained in this application to be confidential, and its contents are not to be disclosed without express written consent.

Please address any questions or comments on this application to :

Mr. Jerry Klimek
Manager, Regulatory Affairs
(201) 503-8145

Sincerely,

Hedy M. Ries
Executive Director,
Drug Registration and
Regulatory Affairs

Attachments: Form FDA 356H
Volumes 1-506

Submitted in duplicate

EXHIBIT VIII

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 29 1994

NDA 20-240

Sandoz Pharmaceuticals Corporation
Attention: Mr. Jerry Klimek
59 Route 10
East Hanover, NJ 07936-1080

Dear Mr. Klimek:

Please refer to your December 30, 1991 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Renormax (spirapril hydrochloride) 3, 6, 12, and 24 mg. Tablets.

We acknowledge receipt of your amendments and correspondence dated May 5, June 8 and 26, July 1 and 22, August 6, September 11, 15 and 17, November 5 and 24, December 3 and 8, 1992; January 26, May 7, 13, 18, 27 and 28, June 8, 15, 18, 29 and 30, July 2, 22 and 23, August 4, 1993; February 3 and 17, June 3, August 8, 12 and 29, September 6 and 15, November 1, and December 6, 21 and 23, 1994.

This new drug application provides for the use of Renormax (spirapril hydrochloride) in the treatment of hypertension.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit fifteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-240. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Any advertising or promotional materials for the use of Renormax (spirapril hydrochloride) Tablets should include the third paragraph from the **INDICATIONS AND USAGE** section.

We understand following our meeting of December 8, 1994, that you have agreed to to reanalyze the data from placebo-controlled titration studies using NONMEM or a similar approach to better define the dose-response relationship and to perform a separate analysis of the data, comparing black and non-black patients. In addition, you have agreed to meet with the Division of Cardio-Renal Drug Products to discuss doing further studies to better define the dose-response relationship.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

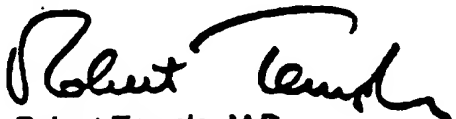
Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
(301) 594-5300

Sincerely yours,



Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

EXHIBIT IX

Case No. 2276

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

ELIJAH H. GOLD et al

For Patent for:
7-CARBOXYALKYLAMINOACYL-1,4-DITHIA-7-AZASPIRO[4.4]NONANE-8-CARBOXYLIC ACID

Serial No.: 446,999

Filed: December 6, 1982

Group No.: 126

Kenilworth, New Jersey 07033

January 25, 1983

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

REQUEST FOR RECORDAL OF ASSIGNMENT

UNDER RULE 331

Please record the accompanying deed of assignment for the above identified patent application on the Assignment Record of the United States Patent and Trademark Office.

Please return the recorded assignment to:

ANITA W. MAGATTI
Schering-Plough Corporation
Patent Department
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Charge the $20.00 fee for recording this assignment and any other fee incident with this assignment to Deposit Account No. 19-0365. A duplicate copy of this document is enclosed for this purpose.

Respectfully submitted:

00563 02/01/83 446929 19-0365 1 516 20.00CH

Anita W. Magatti
Attorney for Applicant
Registration No. 29825
Tel. No. (201) 558-4662

91105779

2270

ASSIGNMENT

(Utility)
Joint

For good and valuable consideration paid to us, (1) Elijah H. Gold

(2) Bernard R. Neustadt (3) Elizabeth M. Smith

(4) _____ of, respectively (1) West Orange, New Jersey

(2) West Orange, New Jersey (3) Verona, New Jersey

(4) _____ by SCHERING CORPORATION, a corporation organized under the laws of the State of New Jersey, having its principal office at Galloping Hill Road, Kenilworth, New Jersey 07033 (hereinafter called "SCHERING"), we each do hereby sell, assign and set over unto said SCHERING each of our entire right, title and interest in all countries of the world in and to any and all of our inventions and discoveries in 7-AMINOACYL-1,4-DITHIA-7-AZASPIRO-[4.4]NONANE-8-CARBOXYLIC ACIDS

as described and/or claimed in our application for United States Letters Patent, executed on December 3, 1982 by Elijah H. Gold and Bernard R. Neustadt and on December 3, 1982 by Elizabeth M. Smith.

and subsequently* officially identified as Serial Number 446,929 filed on 12/06/82, in and to the right to file patent applications in the name of SCHERING, its designee, or in any or all of our names, at its election, on the aforesaid inventions and discoveries in all countries of the world, together will all rights of priority in the aforesaid countries deriving from the above-identified United States patent application under the International Convention for the Protection of Industrial Property, under the Inter-American Convention relating to Inventions, Patents, Designs and Industrial Models and under any other international arrangement to which the United States now is or hereafter becomes a signatory, in and to any and all Letters Patent that issue on any of the aforesaid patent applications, and in and to any reissues, renewals and extensions thereof of any of said Letters Patent, the same to be held and enjoyed by said SCHERING, its successors, assigns and other legal representatives, to the full ends of the terms for which all Letters Patent therefor may be granted, as fully and entirely as the same would have been held and enjoyed by us if this assignment and sale had not been made.

And we Hereby Covenant and agree that we will at any time, upon the request and at the expense of SCHERING, execute and deliver any and all documents that may be necessary or desirable to perfect the title to the foregoing inventions and discoveries, patent applications, and Letters Patent and reissues, renewals and extensions thereof in SCHERING, its successors, assigns or other legal representatives, including the execution and procurement of any and all further documents evidencing this assignment and sale as may be necessary or desirable for recording the same in the Patent Office of any country concerned, and that we will, at any time, upon the request and at the expense of SCHERING, execute any additional or divisional applications for patents for said inventions and discoveries, or any part or parts thereof, and applications for patents of confirmation, registration and importation based on said Letters Patent and on Letters Patent issuing from said additional divisional applications and reissues, renewals and extensions therefor, and will make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein, without further compensation, but at the expense of SCHERING, its successors, assigns or other legal representatives.

*We hereby authorize SCHERING to insert in this instrument the serial number and the filing date of said application for United States Letters Patent when officially notified thereof.

Executed this 3rd day of December, 19 82.

Elijah H. Gold L.S.
Elijah H. Gold

Executed this 3rd day of December, 19 82.

Bernard R. Neustadt L.S.
Bernard R. Neustadt

Executed this 3rd day of December, 19 82.

Elizabeth M. Smith L.S.
Elizabeth M. Smith

Executed this 3rd day of December, 19 ____.

_____ L.S.

REEL 4088 FRAME 256

(Utility)
Joint

Acknowledgement

State of NEW JERSEY)
) s.s:
County of ESSEX)

On this 3rd day of DECEMBER, 19 82.

personally appeared before me Elijah H. Gold
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

(Seal)

Jo Ann O'Dell
NOTARY PUBLIC

JO ANN O'DELL
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires Aug. 9, 1984

Acknowledgement

State of NEW JERSEY)
) s.s:
County of ESSEX)

On this 3rd day of DECEMBER, 19 82.

personally appeared before me Bernard R. Neustadt
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

(Seal)

Jo Ann O'Dell
NOTARY PUBLIC

JO ANN O'DELL
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires Aug. 9, 1984

REEL 4088 FRAME 257

Acknowledgement

State of NEW JERSEY)
) s.s:
County of ESSEX)

On this 3rd day of DECEMBER, 19 82.

personally appeared before me Elizabeth M. Smith
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

(Seal)

RECORDED
PATENT & TRADEMARK
JAN 28 1983

Jo Ann O'Dell
NOTARY PUBLIC

JO ANN O'DELL
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires Aug. 9, 1984

Acknowledgement

State of Bernard W. Kennedy, Jr.
COMMISSIONER OF PATENTS AND TRADEMARKS
) s.s:
County of _____)

On this _____ day of _____, 19____.

personally appeared before me _____
to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he or she executed the same, of his or her own free will for the purpose set forth.

(Seal)

_____
NOTARY PUBLIC

2276 APRIL 23, 1992
U.S.

UNITED STAT)DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

90

EXHIBIT X

PAYOR NUMBER
000225

DENNEMEYER & CO. LTD.
REGENT HOUSE, HEATON LANE
STOCKPORT
CHESHIRE, ENGLAND, SK4 1BB NY

DATE MAILED
04/08/92

212996

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,470,972	184	1810	----	06/446,929	09/11/84	12/06/82	08	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	US 2276

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

PTO 439 (REV 4 88)

EXHIBIT XI

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-240

Sandoz Pharmaceuticals Corporation
Attention: M.J. Finkel, M.D.
59 Route 10
East Hanover, NJ 07936

RECEIVED
JAN 16 1992
MARION J. FINKEL, M.D
VICE PRESIDENT/DRA

JAN 13 1992

Dear Dr. Finkel:

We have received your new drug application submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Drug Product: Spirapril Hydrochloride Tablets

Date of Application: December 30, 1991

Date of Receipt: December 31, 1991

Our Reference Number: NDA 20-240

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b)(1) of the Act on February 28, 1992 in accordance with 21 CFR 314.101(a).

If the application is filed, the due date will be June 29, 1992.

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact:

Ms. Kathleen Bongiovanni
Consumer Safety Officer
(301) 443-4730

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

EXHIBIT XIIa

CHRONOLOGY OF IND REGULATORY ACTIVITIES FOR RENORMAX® (spirapril hydrochloride) TABLETS

DATE	TYPE	DESCRIPTION
12/22/83	Submission to FDA	Cover letter from Schering transmitting to FDA the IND for Sch 33844 Hydrochloride Oral including Study #C83-099-01 conducted under the direction of Dr. William J. Flanigan
1/11/84	FDA Letter	Acknowledges receipt on 12/23/83 of Schering IND and assigns IND No. 23,278
2/27/84	Submission to FDA	Letter from Schering amending the protocol of Study #C83-099-01 to incorporate changes thereto and provide outstanding documentation in support of the Study
3/26/84	Submission to FDA	Letter from Schering providing (1) a second amendment to the protocol of Study #C83-099-01 submitted 2/27/84 and (2) amendments to Attachments 2, 3, 4 and 5 of subject IND
11/5/84	FDA Letter	FDA request for submission by Schering of certain additional information when subject IND enters Phase III clinical studies
1/21/85	Submission to FDA	Letter from Schering submitting the Schering progress report on the subject IND regarding Attachments 5, 6 and 10
2/7/85	Submission to FDA	A letter from Schering acknowledging receipt of FDA letter dated 11/5/84 requesting certain information and informing FDA that protocol submitted in the original IND on 12/22/83 represents initial trial in Phase II of clinical pharmacology and that FDA requests and recommendations will be addressed when Phase III clinical trials are initiated

DATE	TYPE	DESCRIPTION
6/26/85	Submission to FDA	Letter from Schering (1) amending subject IND to include Study #S85-006-02 to be conducted by Dr. Robert Reeves as a safety and efficacy study of Sch 33844 versus captopril and (2) amending the subject IND by including new amendments to Attachments 2, 3 and 5
6/28/85	Submission to FDA	Letter from Schering providing responses to each of questions raised in FDA letter dated 11/5/84 regarding recommended specification for when Sch 33844 enters Phase III clinical studies
7/10/85	Submission to FDA	Letter from Schering amending the subject IND to include two additional study centers: (1) Study #S85-006-01 under the direction of Dr. Richard Katz and (2) Study #S85-006-03 under the direction of Dr. James Gray
7/12/85	Submission to FDA	Letter from Schering amending subject IND to include Study #S85-006-05 under the direction of Dr. Albert Dietz
7/22/85	Submission to FDA	Letter from Schering amending the subject IND to include two additional study centers: (1) Study #S85-006-04 under the direction of Dr. Luther Clark and (2) Study #S85-006-06 under the direction of Dr. Michael Weber
8/6/85	Submission to FDA	Letter from Schering amending the subject IND to include an additional Study #S85-006-07 under the direction of Dr. John Nadeau
3/6/86	Submission to FDA	Letter from Schering submitting the progress report for the subject IND including updated stability report, preclinical reports, a curriculum vitae for current project physician and a clinical report

DATE	TYPE	DESCRIPTION
3/10/86	Submission to FDA	Letter from Schering reporting that patient enrolled in Study #S85-006-06 experience an adverse reaction (pulmonary edema) while being treated with captopril
4/2/86	Submission to FDA	Letter from Schering amending the subject IND to include Study #C85-079-01 under the direction of Dr. Albert Cohen
4/25/86	Submission to FDA	Letter from Schering informing the Division of Cardio-Renal Drug products that the progress report submitted by Schering on 3/6/86 which was inadvertently sent to the Division of Anti-Infective Drugs was now being forwarded to the Division of Cardio-Renal Drugs
5/1/86	Submission to FDA	Letter from Schering notifying the transfer of IND sponsorship to Sandoz
5/29/86	Submission to FDA	Sandoz confirms responsibility of transfer obligations. Compound now referred to as TI 211-950 Capsules
5/30/86	Submission to FDA	Protocol for Study No. 1
6/9/86	FDA Letter	Acknowledges Sandoz sponsorship of IND; requires documentation due to change in ownership (ie, new FD Form 1571, assurance all investigators have been informed of the change)
7/15/86	Submission to FDA	Response to 6/9/86 letter
8/7/86	Submission to FDA	Protocol for Study No. 10
9/22/86	Submission to FDA	Manufacturing update naming Sandoz as the manufacturer of the dosage form
9/23/86	Submission to FDA	Protocol for Multicenter Study No. 2 - Centers A & E

DATE	TYPE	DESCRIPTION
9/25/86	Submission to FDA	Amend Multicenter No. 2- Center E to provide for the determination of effects of study drug on ambulatory blood pressure and heart rate at various weeks.
9/29/86	Submission to FDA	Multicenter Study No.2 - New Study Center D
10/9/86	Submission to FDA	Multicenter Study No.2 - New Study Center F
10/9/86	Submission to FDA	Multicenter Study No.2 - New Study Center G
10/15/86	Submission to FDA	Amend Study No. 10 to provide for long term administration of TI 211-950
10/17/86	Submission to FDA	Multicenter Study No.2 - New Study Center C
10/21/86	Submission to FDA	Amend Multicenter Study No.2 - Center D to investigate effects of study drug on the renin-angiotensin - aldosterone system
10/21/86	Submission to FDA	Protocol for Study No. 3
11/4/86	Submission to FDA	Manufacturing amendment to provide for a 1 mg/ml strength oral reference solution
11/12/86	Submission to FDA	Amend Muticenter Study No. 2 - Center F to provide for the evaluation of the blood pressure lowering effect of TI 211-950 and placebo
11/13/86	Submission to FDA	Multicenter Study No. 2 - New Study Center B
12/12/86	Submission to FDA	Protocol for Study No. 4 and particle size data used in this study
12/30/86	Submission to FDA	Manufacturing update to include a limit of 5% for the diketopiperazine degradation product. Acute tox study is included as the basis for this limit

DATE	TYPE	DESCRIPTION
12/30/86	Submission to FDA	Human Pharmacokinetic Study Reports/RIA Report
1/7/87	Submission to FDA	Amend Multicenter Study No. 2 - Center D to provide for long term administration of TI 211-950
1/13/87	Submission to FDA	Safety Report on a patient discontinuance due to irregular pulse rates.
1/14/87	Submission to FDA	Amend Multicenter Study No. 2 - Center B to provide for long term administration of TI 211-950
1/15/87	Submission to FDA	Amend Multicenter Study No. 2 - Center C to provide for long term administration of TI 211-950
1/15/87	Submission to FDA	Amend Multicenter Study No. 2 - Center F to provide for long term administration of TI 211-950
1/18/87	Submission to FDA	Manufacturing amendment to provide for radioactive TI 211-950
1/19/87	Submission to FDA	Follow-up from investigator on safety report 1/13/87
1/19/87	Submission to FDA	Protocol for Study No. 6
2/19/87	Submission to FDA	Safety Report on a patient with a preliminary diagnosis of left sided heart failure.
3/2/87	Submission to FDA	Safety Report - Death Notification
3/5/87	Submission to FDA	Protocol for Study No. 11
3/10/87	Submission to FDA	Letter of cross reference to Sandoz' IND on behalf of an investigator to file a private IND
3/11/87	Submission to FDA	Amend Study No. 11 to provide for long term administration of TI 211-950
3/16/87	Submission to FDA	Follow-up from investigator on safety report 2/19/87

DATE	TYPE	DESCRIPTION
3/17/87	Submission to FDA	Follow-up from investigator on safety report 3/2/87
3/24/87	Submission to FDA	Protocol for Study No. 12 - Center 1
4/1/87	Submission to FDA	Study No. 12 - New Study Centers 2, 3, 4 & 5
4/1/87	Submission to FDA	Preclinical Reports - Perinatal and Postnatal Reproduction Studies
4/6/87	Submission to FDA	Study No. 12 - New Study Center 6
4/10/87	Submission to FDA	Preclinical Report - Acute Toxicity Study
4/22/87	Submission to FDA	Safety Report on a patient who experienced pronounced facial edema and difficulty with swallowing.
4/27/87	Submission to FDA	Manufacturing amendment to update NDS section
5/7/87	Submission to FDA	Manufacturing amendment to update NDS section
5/18/87	Submission to FDA	Study No. 12 - New Study Center 7
5/28/87	Submission to FDA	Study No. 12 protocol replacement page
5/28/87	Submission to FDA	Study No. 12 - New Study Center 8
6/3/87	Submission to FDA	Safety Report on a patient who was hospitalized due to angioedema of the epiglotis, tongue and pharyngeal area
6/5/87	Submission to FDA	Safety Report on a patient who was hospitalized due to gastrointestinal bleeding
6/16/87	Submission to FDA	Follow-up from investigator on safety report 6/3/87
6/18/87	Submission to FDA	Annual Progress Report

DATE	TYPE	DESCRIPTION
6/19/87	Submission to FDA	Amend Study No. 11 to provide for a modification in the entrance requirement
6/19/87	Submission to FDA	Amend Study No. 12 - Center 7 to provide for testing the hypothesis that Spirapril may possess the ability to reduce the complexity and frequency of ventricular arrhythmia
7/9/87	Memo of Record (FDA Telephone Call)	IND requirements on an IV formulation of Spirapril
7/20/87	Submission to FDA	Manufacturing update providing for a revised formulation in which Maleic Acid has been added in place of a portion of the lactose
7/21/87	Submission to FDA	Amend Study No. 10 to provide for a modification in the patient entrance criteria
7/30/87	Submission to FDA	Study No. 12 - New Study Center 9
7/31/87	Submission to FDA	Amend Study No. 12 to provide for long term administration of TI 211-950
7/31/87	Submission to FDA	Study No. 2 - Center B New Subinvestigators
8/10/87	Submission to FDA	Amend Study No. 12 - Center 4 to provide for long term administration of TI 211-950
8/10/87	Submission to FDA	Amend Study No. 11 to provide for a test dose of Spirapril to be included during the screening period and prior to dispensing higher dose levels
8/10/87	Submission to FDA	Amend Study No. 10 to provide for a test dose of Spirapril to be included during the screening period and prior to dispensing higher dose levels

DATE	TYPE	DESCRIPTION
8/11/87	Submission to FDA	Study No. 10 - New Subinvestigator
9/2/87	Submission to FDA	Protocol for Study No. A108
9/11/87	Submission to FDA	Amend Study No. 12 - Centers 1-7 & 9 to provide for a test of captopril during the stabilization period
9/16/87	Submission to FDA	Study No. 12 - New Study Center 10
9/16/87	Submission to FDA	Study No. A108 - New Subinvestigator
9/16/87	Submission to FDA	Protocol for Study B301 - Center No. 2
9/29/87	Submission to FDA	Study B301 - New Study Center 3
10/7/87	FDA Letter	Clinical, drug metabolism and compound nomenclature requests and recommendations
10/14/87	Submission to FDA	Letter of cross reference to Sandoz' IND on behalf of an investigator to file a private IND
10/16/87	Submission to FDA	Study B301 - New Study Centers 4,5,6,12 &13
10/20/87	Submission to FDA	Amend Study B301 - Center 6 to provide for long term administration of TI 211-950
10/28/87	Submission to FDA	Amend Study No. B301 - Center 3 to provide for evaluating the blood pressure lowering effect of five fixed doses of Spirapril compared to placebo
10/28/87	Submission to FDA	Amend Study B301 - Centers 3 & 6 to allow for several revisions in the protocol
12/14/87	Submission to FDA	Protocol for Study No. A109
12/21/87	Submission to FDA	Protocol for Study No. B314

DATE	TYPE	DESCRIPTION
12/21/87	Submission to FDA	Protocol for Study No. A110
12/30/87	Submission to FDA	Response to FDA request of 10/7/87
1/27/88	Submission to FDA	Protocol for Study No. B318
3/11/88	Submission to FDA	Protocol for Study No. A009
3/11/88	Memo of Record (FDA Meeting)	Use of Glycine HCl as a stabilizer in TI 211-950 formulations
3/14/88	Submission to FDA	Study No. B314 New Study Center 3 and a chemistry, manufacturing & controls amendment
3/15/88	Memo of Record (FDA Visit)	Use of TI 211-950 in women of child-bearing potential
3/23/88	Memo of Record (FDA Telephone Call)	Request to provide a more detailed explanation of manufacturing submission dated 3/14/88
4/5/88	Submission to FDA	Safety Report of a non-US adverse reactions received from Basel
4/5/88	Submission to FDA	Response to request of 3/23/88
4/5/88	Submission to FDA	Protocol for Study B317 - Centers 4 & 5. Toxicology reports.
4/7/88	Submission to FDA	New study centers for Studies 12 - Center 11, A109 - Center 2, B301 - Centers 8 & 11, B314 - Centers 2,5, & 7, and B318 - Center 2. Amend Study No. 12 -Center 8 to provide for long term administration of TI 211-950. Amend Study No. B314 to provide for long term administration of TI 211-950. Manufacturing update. Toxicology and drug metabolism reports. New subinvestigators for Study No. 2, Center G and Study No. 12, Center 5.

DATE	TYPE	DESCRIPTION
4/13/88	Memo of Record (FDA Telephone Call)	Regarding use of Spirapril in women of child-bearing potential
4/18/88	Memo of Record (FDA Telephone Call)	Regarding serial number error.
4/20/88	Memo of Record (FDA Telephone Call)	Regarding the non-US adverse reactions report submitted on 4/5/88
4/22/88	Submission to FDA	Amend Study No. A009 to provide for long term administration of TI 211-950 and to provide the investigator the choice of using either inulin or TC99 m - DTPA to measure glomerular filtration rate. Amend Study No. 12 to provide for a revised Appendix. Amend Study No. A109 - Center 1 to revise the Exclusion Criteria and an appendix. Add study centers to Study No. 12 - Center 12 and Study No. B317 - Center 2. Add new subinvestigator for Study No. B301 - Center 8. Toxicology report.
5/9/88	Submission to FDA	Response to FDA request of 4/20/88 on safety report
5/24/88	Submission to FDA	Amend Study No. B314 - Center 5 to provide for 24-hour ambulatory blood pressure monitoring. Amend Study No. B317 - Center 5 to provide for the evaluation of pulmonary function
6/7/88	Submission to FDA	Protocol for Study A012. Amend Study No. 12 - Center 12 to provide for changing the dose levels of TI 211-950 and for Centers 1, 2, 4, 5, 7, 11 and 12 to provide for changes in concomitant medications. Amend Study B317 - Center 4 to investigate effects of study drug on the renin-angiotensin - aldosterone system

DATE	TYPE	DESCRIPTION
6/13/88	Submission to FDA	Study No. 12 new study centers 13 & 14. Study No. B317 new study centers 1 & 3. Study No. B318 new study centers 3 & 4. Amend Study B314 to provide for evaluating the blood pressure lowering effect of five fixed doses of Spirapril compared to placebo. Amend Study B317 to accommodate personal schedule of patients. Study No. 12 - Center 10 add new subinvestigator. Manufacturing update in the hydrochlorothiazide capsule formulation. Toxicology reports.
7/13/88	Submission to FDA	Manufacturing update to include glycine hydrochloride as a new excipient in TI 211-950 tablet formulations. Response to March 11, 1988 meeting.
7/20/88	Submission to FDA	Protocol for Study No. A011
7/21/88	Submission to FDA	Letter authorizing FDA to cross reference our IND on behalf of Schering-Plough since Schering plans to file an IND for an IV form of TI 211-950
7/22/88	Submission to FDA	Protocol for Study A010
7/25/88	Memo of Record (FDA Telephone Call)	Acknowledge receipt of 7/13/88 amendment
7/26/88	Submission to FDA	Annual Report
8/3/88	Submission to FDA	Study No. B316 New Study Centers 1 & 4. Study No. A010 New Study Center 4. Study No. B314 New Study Center 1. Amend Study No. 12 in 2 centers. Amend Study No. B301 to provide for long term administration of TI 211-950. New subinvestigators for Studies B301 and 12. Provide for a new laboratory for Study No. B317 - Center 2.

DATE	TYPE	DESCRIPTION
8/15/88	Submission to FDA	Amend Study A010 - Centers 2 & 3 to revise inclusion criteria and humoral effects. Amend Study B314 - Center 7 to study the calcium homeostatis in relation to ACE inhibition. Amend Study B316 - Centers 2 & 4 to provide for long term administration of TI 211-950. Amend Study B316 to evaluate the effects of the study drugs on the plasma lipoprotein profile
8/22/88	Submission to FDA	Protocol for Study No B313.
9/6/88	Submission to FDA	Amend Study No. 11 to provide for the safety and acute hemodynamic effects of an additional dose level. Study No. B313 new study centers 4, 11 and 14. Study No. B301 new principal investigator.
9/6/88	Submission to FDA	Study No. B313 new study center 8
9/14/88	Submission to FDA	Confirmation of Sandoz/FDA meeting to discuss attached draft protocol for an acute myocardial infarction study. Agenda also included
9/30/88	Memo of Record (FDA Telephone Call)	Request background information regarding draft protocol submitted on 9/14/88
9/22/88	Submission to FDA	Study No. B313 new study centers 2, 3, 5, 6, 10, and 12. Amend Study B314 - Center 1 to allow for the assessment of the effects of TI 211-950 on the limb and cardiac hemodynamic parameters. Amend Study A010 - Centers 1, 4 and 5.
10/4/88	Memo of Record (Sandoz/FDA Meeting Report)	Sandoz' report of meeting with the FDA's comments and suggestions on the draft protocol submitted 9/14/88

DATE	TYPE	DESCRIPTION
10/4/88	Memo of Record (Sandoz/FDA Meeting Report)	FDA's report of meeting to discuss draft protocol
10/7/88	Submission to FDA	Amend Study No. B301 - Centers 9 and 14 to evaluate the blood pressure lowering effect of fixed doses of Spirapril compared to placebo. Study No. B313 new study center 13. Study No. B314 new subinvestigator for Center 6.
10/12/88	FDA Letter	Questions regarding the chemistry, manufacturing and controls section of the original IND and amendment dated July 13, 1988.
10/25/88	Submission to FDA	Protocol for Study No. B321. Amend Study No. A011 to provide for a modification of the blood pressure measurement procedure. Four amendments to Study No. 12 - Centers 3 and 14. Amend Study B314 Center 6 to provide for long term administration of TI 211-950. Study No B313 new study center 1. Study A010 - Center 5 add new subinvestigator. Study B313 - Center 11 change in IRB
11/2/88	Memo of Record (FDA Telephone Call)	Discussion on ongoing clinical program and collection of peak/trough data.
11/11/88	Submission to FDA	Protocol for Study No. B122. Study No. 12 - Center 6 amendment. Study No. B313 new study center 7 and for center 9 new subinvestigator
11/21/88	Submission to FDA	Informed FDA that a letter had been recently sent to all investigators participating in ongoing trials with TI 211-950 notifying them of the occurrence of angioneurotic edema in eight black patients

DATE	TYPE	DESCRIPTION
11/23/88	Submission to FDA	Amend Study No. 2- Center C to modify the maximum recommended dose use in the open-label phase. Amend Study No. B314 - Center 6 to modify the maximum recommended dose use in the open-label phase.
11/29/88	Memo of Record (FDA Telephone Call)	Medical Reviewer called regarding the eight reports of angioneurotic edema submitted 11/21/88 and therefore concerned with amendments providing for a maximum dose
11/30/88	Memo of Record (FDA Telephone Call)	Sandoz' clinical expert called the Medical Reviewer to discuss the concerns expressed in the 11/19 telephone call. FDA requests were made for tabulation of the dose and temporal information; informed consent should be revised to reflect this information; and a recommendation to re-emphasize to investigators the need to discontinue TI 211-950 in case of swelling or hives
12/1/88	Submission to FDA	Letter of cross reference to Sandoz' IND on behalf of an investigator to file a private IND
12/2/88	Memo of Record (FDA Telephone Call)	Resulting from the angioneurotic cases reported, FDA has requested additional information to include halflife of TI 211-950 and blood pressure response for those patients experiencing this adverse reaction

DATE	TYPE	DESCRIPTION
12/8/88	Submission to FDA	Protocol for Studies A013, B123 and B124. Amend Study No. 2 - Center D to provide for long term administration of TI 211-950. Amend Study No. 12 for Centers 1, 3, 7, 8, 10, 11, 12 to modify maximum dosage used in long term phase. Amend Study B301 - Centers 2, 5, 6, 7 and 11 to modify maximum dosage used in long term phase. Amend Study B314 to provide for long term administration of TI 211-950. Study No. B321 new study center. Study No. B301 - Center 2 new subinvestigator
12/16/88	Submission to FDA	Response to FDA requests of November 29 and December 2, 1988.
12/22/88	Memo of Record (FDA Telephone Call)	FDA reviewed the 12/16/88 submission and noted that Sandoz' actions have been appropriate. Two additional requests for information were made: revise patient consent form about the findings of angioneurotic edema and to try and establish why this adverse reaction occurred in blacks.
1/20/89	Submission to FDA	Amend Study No. 2 - Center F to provide for long term administration of TI 211-950. Amend Study No. 12 - Center 5 to provide for long term administration of TI 211-950 and Center 7 to modify maximum dosage used in long term phase. Amend Study No. B301 - Centers 4, 8, 9, 14 to provide for long term administration of TI 211-950. Amend Study B314 - Center 1 to assess the effects of TI 211-950 on limb and cardiac hemodynamic parameters. Amend Study No. B321- Centers 2, 4 and 5 to provide for the long term administration of TI 211-950. Study No. B301 - Center 1 new subinvestigator. Study No. B318 - Center 1 new subinvestigator. Study No. B123 curriculum vitae of subinvestigators inadvertently omitted from previous submission.

DATE	TYPE	DESCRIPTION
1/23/89	Submission to FDA	In response to FDA request of December 22, 1988, a copy of a recent follow-up letter to investigators to update them on the angioneurotic edema issue as well providing them with a proposed text for modifying the patient consent form was provided
1/26/89	Memo of Record (FDA Telephone Call)	Sandoz request for clarification on 2 points raised in FDA letter of October 12, 1988
1/30/89	Submission to FDA	Amend Study No. 12 - Centers 2 and 13 to provide for long term administration of TI 211-950. Amend Study No. B321 - Centers 3 and 6 to provide for long term administration of TI 211-950. Study No. 12 new Center 15. Study B124 replacement pages for case report forms.
2/3/89	Submission to FDA	Amend Study No. 12 - Centers 1, 3, 6, 8, 11, 12 and 14 to provide for long term administration of TI 211-950. Study No. B317 - Center 3 new subinvestigator
2/13/89	Submission to FDA	Amend Study No. 11 to modify maximum dosage used in long term phase. Amend Study No. B301 to restrict the enrollment of new patients to non-black patients only. Amend Study No. B321 - Center 3 to allow for the performance of M-mode echocardiography to assess the effects of the study drug on left ventricular function. Study No. B301 additional study site and new subinvestigator.
2/14/89	Submission to FDA	Response to a request from the FDA Division of Scientific Investigations on 2/13/89 for completed case report forms from Study No. 10.

DATE	TYPE	DESCRIPTION
2/16/89	Submission to FDA	Amend Study No. A009 to allow a reduction in the length of time of the single-blind outpatient placebo period. Amend Study No. 2 to revise the entry criteria. Amend Study No. B122 to revise exclusion criteria and materials and methods.
2/21/89	Submission to FDA	Amend Study No. 12 - Centers 5 and 10 to allow for long term administration of TI 211-950. Amend Study No. A010 - Centers 1 and 5 to restrict the enrollment of black patients. Amend Study No. A013 to restrict the enrollment of black patients. Amend Study No. B301 - Center 5 protocol. Amend Study No. B313 to restrict the enrollment of black patients. Study No. B314 new subinvestigator
3/3/89	Submission to FDA	Amend Study No. 2 - Center 2 to allow for long term administration of TI 211-950. Amend Study No. B314 to restrict the enrollment of black patients. Study No. 12 new study center 16.
3/14/89	Submission to FDA	Protocol for Study No. B126
3/27/89	Submission to FDA	Amend Study No. 10 to reduce the maximum dose of Spirapril in the long term phase.
4/12/89	Submission to FDA	Amend Study No. 12 - Center 16 to modify entrance criteria. Amend Study A010 - Centers 2 and 4 to restrict the enrollment of black patients. Amend Study A011 to restrict the enrollment of black patients. Amend Study No. A012 to restrict the enrollment of black patients. Amend Study A013 to revise the time of initial study drug administration. Study No. A010 - Center 2 new subinvestigator and correct investigator's address.

DATE	TYPE	DESCRIPTION
4/19/89	Submission to FDA	Amend Study No.12 - Center 13 to modify dosage in long term phase. Amend Study No. B123 to restrict enrollment of black patients. Study No. A013 new subinvestigator.
5/17/89	FDA Letter	FDA finds glycine hydrochloride an acceptable inactive ingredient. Reference is made to original amendment dated 5/17/88
5/18/89	Submission to FDA	Amend Study No. 10 to change dosage strength in long term phase. Amend Study A009 to restrict the enrollment of black patients. Amend Study No. A010 - Center 3 to restrict the enrollment of black patients. Study No. B301 - Center 7 new principal investigator and subinvestigators. Study No. B318 new principal investigator and subinvestigator. Study No. B313 new subinvestigator
5/22/89	Submission to FDA	Amend A013 to clarify essential baseline evaluations. Study No. 12 - Center 10 change in drug shipment address.
5/31/89	Submission to FDA	Amend Study B301 - Centers 1-4, 9 and 14 to restrict enrollment of black patients. Amend Study B313 - Centers 1-3, and 6-14 to restrict enrollment of black patients. Amend Study No. B314 - Centers 2-7 to restrict the enrollment of black patients. Amend Study No. B316 - Centers 2 and 4 to restrict enrollment of black patients. Amend Study No. B317 - Centers 2-4 to restrict enrollment of black patients. Amend Study No. B318 - Centers 1-3 to restrict enrollment of black patients. Amend Study No. B321 - Centers 3, 5 and 6 to restrict enrollment of black patients.

DATE	TYPE	DESCRIPTION
6/15/89	Submission to FDA	Amend Study B313 - Center 7 to restrict the enrollment of black patients.
6/16/89	Submission to FDA	Manufacturing amendment to update the tablet and capsule manufacture and to provide for a positive control. (Partial response to FDA request of October 6, 1988)
6/19/80	Submission to FDA	Study No. 12 new study Center 17
7/14/89	Submission to FDA	Protocol for Study No. B125. Manufacturing update on additional formulations
8/7/89	Submission to FDA	Annual Report
8/9/89	Submission to FDA	Amend Study A011 - Center 1 to modify exclusion criteria, add center 2, and to include pulmonary function studies. Amend Study B313 -Center 2 to restrict the number of black patients. Amend Study B316 - Center 1 to restrict the enrollment of black patients and Center 4 to modify evaluation times. Amend Study B321 - Center 2 to restrict the enrollment of black patients. Study B313 -Center 6 new principal investigator. Study A010 new study Center 2. Study 12 - Center 17 new drug shipment address. New subinvestigators for Study No. 12 - Center 7, Study No. B125 and Study A010 -Centers 2 and 5.
8/10/89	Submission to FDA	Response to FDA request of October 6, 1988 in the area of chemistry, manufacturing & controls. (A partial response was also submitted June 16, 1989)
8/18/89	FDA Letter	FDA lists pharmacokinetic issues raised as a result of our December 30, 1986 submission.

DATE	TYPE	DESCRIPTION
8/23/89	Submission to FDA	Amend Study B316 to compare Spirapril, ACE inhibitor against those of a diuretic. Study No. 12 - Center 17 change of investigator's address.
8/29/89	Submission to FDA	Protocol for Study No. B127
9/28/89	Submission to FDA	Amend Study A013 to require additional echocardiographic evaluations. New subinvestigators for Studies No. A010 - Center 4 and B314 - Center 1.
10/12/89	Submission to FDA	Amend Study No. 12 - Centers 7, 11 and 16 to restrict the enrollment of black patients and reduce the maximum dose of TI 211-950 during the long term phase.
10/20/89	FDA Letter	Three requests on chemistry, manufacturing & controls based on August 10, 1989 submission
10/30/89	Submission to FDA	Amend Study No. 12 - Center 10 to restrict the enrollment of black patients, reduce the maximum dose of TI 211-950 during the long term phase, and modify the entrance criteria. Amend Study No. A011-Center 1 and 2 to modify the entrance criteria. Amend Study No. B316 - Center 2 to revise the evaluation schedule. Study No. 12 - Centers 2 and 17 new investigators' address.
11/3/89	Submission to FDA	Amend Study No. 12 - Center 14 to modify entrance criteria.
12/11/89	Submission to FDA	Amend Study No. 12 - Center 12 to modify the study design. Study No. A010 - Center 2 to add new satellite study site. New subinvestigators for Studies No. A010 - Center 2 and Study No. B314 - Center 6.

DATE	TYPE	DESCRIPTION
12/15/89	Submission to FDA	Provide non-clinical documentation for a major metabolite of Spirapril, known as spiraprilat, in order to ship spiraprilat to our parent company in Basel, Switzerland to conduct 2 small safety and pharmacokinetic studies. The studies are not being conducted under the US IND and are not intended to be part of the US registration program.
1/24/90	Submission to FDA	Amend Study No. 6 to reduce the maximum dose of TI 211-950. Amend Study No. 12 - Centers 1-3, 6, 8 and 12-15 to reduce the maximum dose of TI 211-950 during the long term phase and to restrict the enrollment of black patients. Amend Study No. A009 to reduce the maximum dose of TI 211-950 during the long term phase. New subinvestigators for Studies No. 10 and 12.
1/25/90	Submission to FDA	The results of a commitment made in our August 10, 1989 letter in response to an FDA manufacturing and controls question on October 6, 1988.
3/8/90	Submission to FDA	Amend Studies No. B301 - Centers 2, 4, 5-9, and 12, B314 - Centers 1, 3, 5 and 6, B316 - Center 2 and B321 to reduce the maximum dose of TI 211-950.
4/2/90	Submission to FDA	Amend Study No. 12 - Centers 5 and 17 to restrict the enrollment of black patients and reduce the maximum dose of TI 211-950 during the long term phase; change in principal investigator.
5/22/90	Submission to FDA	Study No. 12 - Center 17 change of address.
6/8/90	FDA Letter	Question regarding manufacturing and controls submission of January 25, 1990.

DATE	TYPE	DESCRIPTION
9/28/90	Submission to FDA	Response to June 8, 1990 FDA letter.
11/5/90	Memo of Record (FDA Telephone Call)	A patient contacted the FDA to report an adverse experience while receiving Spirapril. Commitment by Sandoz to follow-up on this patient.
11/6/90	Submission to FDA	Annual Report
11/12/90	Submission to FDA	Studies No. B302 - Center 4 and B321 Center 5 new subinvestigators.
12/11/90	Submission to FDA	Follow-up on November 5, 1990 telephone call regarding safety report.
2/13/91	Submission to FDA	Study B302- Center 9 new principal investigator.
3/28/91	Submission to FDA	Update chemistry, manufacturing and controls section on the new drug substance of Spirapril.
11/12/91	Submission to FDA	Amend Study No. B314 to reduce the maximum dose of Spirapril during the long term phase.
12/20/91	Submission to FDA	Annual Report
1/31/92	Submission to FDA	Study No. 10 new subinvestigator
4/26/92	FDA Letter	Change in Division policy regarding documentation of investigator qualifications
4/27/92	FDA Letter	Requests Sandoz' cooperation and assistance in providing FDA with data files containing ambulatory blood pressure measurements.
5/15/92	Submission to FDA	Safety report regarding the deterioration of renal function in a patient receiving Spirapril in a non-US study.
11/5/92	Submission to FDA	Study No. 10 co-principal investigator

DATE	TYPE	DESCRIPTION
1/15/93	Submission to FDA	Annual Report
5/14/93	FDA Letter	Identifies the final list of data elements and file format for submission of ambulatory blood pressure monitoring data.
7/2/93	FDA Letter	Meeting schedule on ambulatory blood pressure monitoring (ABPM) data project.
7/9/93	FDA Memo	Agenda and background information for ABPM meeting.
8/27/93	FDA Memo	Summary of ABPM meeting
10/7/93	Submission to FDA	Seven (7) diskettes of required SAS data sets which monitored ambulatory blood pressure.
10/18/93	Submission to FDA	Resubmission of ABMP data sets on diskettes compatible with the Agency's DOS version.
3/31/94	FDA Letter	Request to include creatinine phosphokinase (CPK) determinations routinely in patients who become symptomatic (myalgia, back pain etc) during the course of a trial.
4/6/94	Submission to FDA	Annual Report
8/25/94	Submission to FDA	Annual Report

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EXHIBIT XIIb

CHRONOLOGY OF NDA REGULATORY ACTIVITIES FOR RENORMAX® (spirapril hydrochloride) TABLETS

NDA No. 20-240 [TI 211-950 (spirapril hydrochloride) Tablets]		
12/30/91	Submission to FDA	Submission of NDA No. 20-240 [TI 211-950 (spirapril hydrochloride) tablets] to FDA.
1/13/92	FDA Letter	FDA letter acknowledging the official receipt date of the NDA as December 31, 1991, the sixty(60) day filing date is February 28, 1992 and that the 180 day review period would end on June 29, 1992.
1/27/92	Memo of Record (FDA Phone Call)	Division of Scientific Investigation (Clinical Investigation Branch) request for a listing of principal investigators, numbers of patients enrolled per center, and protocols for all US well controlled studies.
2/6/92	Memo of Record (FDA Phone Call)	Notification that the NDA is fileable.
2/13/92	Submission to FDA	Response to FDA request of January 27, 1992 for a listing of principal investigators, numbers of patients enrolled per center, and protocols and amendments for all US well controlled studies.
3/5/92	FDA Letter	FDA letter describes ACE inhibitor class labelling changes to various sections of the package insert
3/13/92	FDA Letter	FDA letter indicates that the FDA has fifteen recommendations/requests concerning the Chemistry, Manufacturing and Controls section of the NDA.
3/20/92 & 3/23/92	Memo of Record (FDA Phone Call)	Statistical Reviewer request for copies of specific statistical summary tables and figures for US Studies B318 and C83-099-01
3/25/92	Submission to FDA	Response to FDA (Biometrics) telephone call of March 23, 1992 requesting specific statistical summary tables and figures for US studies B318 and C83-099-01

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NDA No. 20-240 [TI 211-950 (spirapril hydrochloride) Tablets]		
4/15/92	Memo of Record (FDA Phone Call)	Sandoz indicated that they would be sending the 120 day safety update to the FDA on May 6, 1992 (the FDA accepted).
5/5/92	Submission to FDA	120-Day Safety Update and Revised Draft Labelling.
6/1/92	Memo of Record (FDA Phone Call)	Statistical Reviewer request for information on Study B125 regarding the Schuirmann's Two One-Sided t-test (transformed and untransformed versions).
6/3/92	Memo of Record (FDA Phone Call)	Sandoz called the FDA for clarification of their Statistical Reviewer's request of June 1, 1992 regarding Study B125's confidence intervals.
6/8/92	Submission to FDA	Response to FDA (Biopharmaceutics) telephone call of June 1, 1992 requesting information about the conventional 90% confidence interval for the comparison between the tablet and capsule formulations in Study No. B125.
6/9/92	Memo of Record (FDA Meeting)	Discussion with the Reviewing Chemist concerning deficiencies in the Environmental Assessment
6/15/92 & 6/16/92	Memo of Record (FDA Phone Call)	Chemistry Reviewer inquired if Sandoz had a validated process for manufacture and if Sandoz was prepared for an inspection. Additionally, the Reviewer inquired about the status of Sandoz's response to a FDA letter dated March 13, 1992 and that another FDA letter was to be sent regarding the Environmental Assessment
6/15/92 & 6/16/92	Memo of Record (FDA Phone Call)	Division of Biopharmaceutics request for the calibration curves used in Study A003.
6/16/92 & 6/17/92	Memo of Record (FDA Phone Call)	Division of Biometrics request for SAS data files on diskette including patient number, investigator (center), treatment group, sitting diastolic blood pressure and dose level for Study Nos. B314 and B321.

NDA No. 20-240 [TI 211-950 (spirapril hydrochloride) Tablets]		
6/18/92	Memo of Record (FDA Phone Call)	Division of Biopharmaceutics request for assay validation's for Study Nos. TIA 301-E-00-01, TIA 105, B123 and B124.
6/26/92	Submission to FDA	Response to FDA (Biopharmaceutics) telephone call of June 16, 1992 requesting standard curves for Study A003 and on assay variability for Study A107.
7/1/92	Submission to FDA	Response to FDA (Biometrics) telephone call of June 17, 1992 requesting information on Studies B314 and B321 (SAS data files on diskette including patient number, investigator (center), treatment group, sitting diastolic blood pressure and dose level).
7/2/92	Memo of Record (FDA Phone Call)	Sandoz requested clarification for a Division of Biopharmaceutics request of June 18, 1992 regarding Studies B123 and B124. Also, the Division acknowledged the receipt of their request of June 16, 1992 regarding standard curves for Study A003.
7/7/92	Memo of Record (Sandoz Visitor)	Spirapril Licensing - Visit by Robert Reder, MD (Medical Director, Purdue Frederick Company).
7/8/92	Memo of Record (FDA Letter)	FDA request for information regarding the Environmental Assessment.
7/16/92	Memo of Record (FDA Phone Call)	A request from the Division of Biometrics to provide both the rat and mouse carcinogenicity studies on diskette. Also a fax was sent which described the Division of Biometrics Formats and Specifications for Submission of Animal Tumorigenicity Study Data.
7/22/92	Submission to FDA	Response to FDA (Biopharmaceutics) telephone call of June 18, 1992 requesting assay validation information for Spirapril and Spiraprilat for Study Nos. B123 and B124 and Spirapril alone for Study Nos. TIA 301E-0-001 and TIA 105.

NDA No. 20-240 [TI 211-950 (spirapril hydrochloride) Tablets]		
8/3/92	Submission to FDA	Response to FDA telephone call of July 31, 1992 requesting appendices for Study S-85-006.
8/6/92	Memo of Record (FDA Phone Call)	Division of Biopharmaceutics request for further information for Study Nos. B123 (assay validation data for the kit used to measure Digoxin) and TI A115 (HPLC procedure used to measure Diclofenac).
8/6/92	Submission to FDA	Reference to a teleconference on August 3, 1992 requesting Investigator's and Coinvestigator's CVs for Study No. S85-006.
8/26/92	Memo of Record	FDA audit (5/26-6/1/92) - Spirapril Study B313/6 (J. Hollilfield/D. Pinson - Investigators) - Attachments include a) copy of the FDA 483 report (9/3/92) and b) two(2) follow-up letters from Dr. Pinson regarding the FDA inspection.
9/9/92	Memo of Record (FDA Phone Call)	Chemistry Reviewer had inquired when a pre-approval inspection could be made of the Sandoz Manufacturing facilities, the status of Sandoz's response to Environmental Assessment questions and if Sandoz had a trade name for TI-211-950 (spirapril hydrocholoride). Additionally, an apology was extended to the reviewer regarding responses to a FDA letter dated March 13, 1992.
9/10/92	FDA Letter	Notification from Clinical Pharmacology Associates (Miami, FL) regarding comments from the FDA about the audit the FDA conducted at their office (June 25-29, 1992).
9/11/92	Submission to FDA	Response to FDA [Chemistry, Manufacturing and Controls (CMC)] Request on March 13, 1992 regarding recommendations and requests relative to CMC.
9/15/92	Submission to FDA	Response to FDA (Toxicology) Request on July 16, 1992 regarding animal tumorigenicity data (rat carcinogenicity study information submitted with this submission).

NDA No. 20-240 [TI 211-950 (spirapril hydrochloride) Tablets]		
9/17/92	Submission to FDA	Response to FDA (Biopharmaceutics) Request on August 6, 1992 regarding Diclofenac.
10/7/92 & 10/8/92	Memo of Record (FDA Phone Call)	FDA request to set up a meeting with Sandoz to discuss the development of the Summary for Basis of Approval (SBA).
10/20/92	Memo of Record (FDA Phone Call)	Chemistry Reviewer inquiring if Sandoz had decided where the manufacturing site would be, so the FDA could conduct a pre-approval inspection.
10/30/92	Memo of Record (FDA Meeting)	Sandoz/FDA meeting discussing the preparation of the Summary Basis of Approval.
11/2/92	FDA Letter	FDA letter confirming a FDA meeting with Sandoz to discuss Ambulatory Blood Pressure Data.
11/5/92	Submission to FDA	Response to FDA (Toxicology) telephone call of July 16, 1992 requesting computer diskettes of the animal tumorigenicity data, with accompanying desk copies of the rat and mouse carcinogenicity studies.
11/9/92	FDA Letter	FDA letter which accompanied the Medical Reviewer's 172 page draft review of the NDA. The FDA letter requested that Sandoz address the Reviewer's questions concerning the Summary Basis of Approval.
11/13/92	Memo of Record (FDA Phone Call)	Manufacturing/Controls Issues leading to possible NDA withdrawal were discussed.
11/16/92	Memo of Record (FDA Phone Call)	Sandoz inquired when they would receive the medical and statistical reviews from the Division and discussed the Division's request to withdraw the NDA. The Division advised that they would continue to review the submission even if Sandoz decided to withdraw the NDA (something Sandoz management had not yet decided). Sandoz also requested a meeting to discuss the Chemistry, Manufacturing and Controls amendment.

NDA No. 20-240 [TI 211-950 (spirapril hydrochloride) Tablets]		
11/18/92 & 11/19/92	Memo of Record [FDA Visit (11/18) & FDA Phone Call (11/19)]	Sandoz asked if the "user fee" application would need to be payed if Sandoz withdrew the NDA (a decision to be made by Sandoz on November 27, 1992) and if a meeting could be scheduled to discuss the Chemistry, Manufacturing and Controls amendment that would be required if the product was outlicensed and the manufacturing site changed to Basel. The FDA explained that they were withdrawing their request of November 13 to withdraw the NDA.
11/24/92	Memo of Record (FDA Phone Call)	The Consumer Safety Officer indicated that they could not locate Volumes 491 - 499 of Section 12. Sandoz agreed to send copies to her asap.
12/3/92	Submission to FDA	Response to FDA telephone call of November 24, 1992 requesting Volumes 491-499 of Section 12
12/8/92	Submission to FDA	Response to FDA request for information at meeting held on October 30, 1992 to discuss the Summary Basis of Approval.
1/4/93	Memo of Record (FDA Phone Call)	FDA request that Sandoz fill out Pediatric Use Forms (telefaxed to Sandoz). Notified that FDA that the Summary Basis of Approval would be submitted to the Division by the end of February along with the Safety Update.
1/26/93	Submission to FDA	Response to FDA (Biopharmaceutics) telephone call of August 6, 1992 for the assay validation data for the measurement of Digoxin in Study B123.
3/19/93	Memo of Record (FDA Phone Call)	Sandoz notifies the FDA that the manufacturing site for Spirapril will be Sandoz, East Hanover, NJ. The FDA identifies that a couple of Sandoz's Drug Master File holders have not yet responded to the FDA request for furhter information and request that Sandoz contact them in order to facilitate a response.

NDA No. 20-240 [TI 211-950 (spirapril hydrochloride) Tablets]		
3/25/93	Memo of Record (FDA Phone Call)	FDA Medical Reviewer completes his primary review of the NDA and requests Sandoz submit a Draft Summary Basis of Approval.
3/29/93	Memo of Record (FDA Phone Call)	FDA requests desk copies of the Overall Summary of the NDA and the Integrated Safety Summary.
4/7/93	Submission to FDA	Response to FDA telephone call of March 29, 1993 requesting desk copies of the Overall Summary of the NDA and the Integrated Safety Summary.
4/13/93	Memo of Record (FDA Phone Call)	Sandoz asks FDA if they will accept a "limited" Safety Update with the Draft Summary Basis of Approval. FDA requests that the dissolution profile from the bio lots for the "to be" marketed tablets in water, acid and intestinal fluid be submitted. Additionally, the FDA requested an explanation for using maleic acid to improve stability.
4/14/93	Submission to FDA	Response to FDA telephone call of April 14, 1993 requesting a desk copy of the twenty-two month oral carcinogenicity rat study and the two-year carcinogenicity rat study.
4/21/93	Memo of Record (FDA Phone Call)	Sandoz indicated that they would be sending the dissolution data that the FDA requested and that they would be telefaxing a list of submission dates for all outstanding FDA requests.
4/23/93	Submission to FDA	A list itemizing outstanding information requested by the FDA for the NDA and specific dates when this information would be submitted was telefaxed to the FDA.

NDA No. 20-240 [TI 211-950 (spirapril hydrochloride) Tablets]		
4/26/93	Memo of Record (FDA Phone Call)	FDA is notified that Sandoz is prepared for a pre-approval inspection by the middle to end of June 1993. Sandoz identifies that the Environmental Assessment (EA) will be amended with information from Roberts Pharmaceuticals (prospective licensee).
4/29/94	Memo of Record (FDA Phone Call)	Sandoz requests a copy of the finalized primary medical review.
5/3/93	FDA Letter	The FDA letter refers to questions that the Medical Reviewer had concerning the NDA submission.
5/7/93	Submission to FDA	Response to FDA telefax received on November 24, 1992 requesting information on Studies TI B201, TI B302, TI B305 and TI B305-E-01.
5/10/93	Memo of Record (FDA Phone Call)	FDA asks if Sandoz has established a trade name for TI 211-950
5/12/93	Submission to FDA	Response to FDA (Biopharmaceutics) telephone call of April 13, 1993 requesting dissolution information on biobatches for the marketed TI 211-950 tablets and an explanation for using maleic acid to improve stability.
5/13/93	Memo of Record (FDA Phone Call)	Sandoz informed the FDA that we would be providing the FDA requested information that was specified in the Medical Review, Appendix D. The FDA informed Sandoz that there would be more requested changes to the package insert.
5/14/93	FDA Letter	The FDA letter listed the data elements and file format for submission of ambulatory blood pressure monitoring (ABPM) data.
5/18/93	Submission to FDA	Response to FDA letter dated May 3, 1993. This review contained FDA requests for clinical information as specified in Appendix D.
5/19/93	Submission to FDA	Response to FDA telephone call of May 19, 1993 requesting better copies of tables found in Section 5.

NDA No. 20-240 [TI 211-950 (spirapril hydrochloride) Tablets]		
5/21/93	Submission to FDA	Response to FDA telephone call of January 4, 1993 requesting that Sandoz fill out the Pediatric Use Form.
5/27/93	Submission to FDA	Response to FDA request for information as requested by FDA at meeting held on October 30, 1992.
5/28/93	Submission to FDA	Submission of a Limited Safety Update with revised labelling.
6/2/93	Memo of Record (FDA telephone call)	FDA request for clinical safety data for Study No. TI B329.
6/8/93	Submission to FDA	Submission of clinical safety data for Study No. TI B329.
6/8/93	Memo of Record (FDA telephone call)	FDA request for severity of lesions table in regard to the 21 month oral carcinogenicity study in the mouse (doc. no. 203-217).
6/15/93	Submission to FDA	Formal notification to FDA that the manufacturing site for TI 211-950 (spirapril hydrochloride) Tables is Sandoz Pharmaceuticals Corportation, East Hanover, N.J.
6/18/93	Submission to FDA	Submission of further clinical safety data for Study No. TI B329.
6/29/93	Submission to FDA	Submission of follow-up information on patients that experienced angioneurotic edema and hospital records for Patient No. 358 of Study No. TI B305.
6/30/93	Submission to FDA	Submission in response to FDA request of 6/8/93 for lesion tables for the 21 month oral carcinogenicity study in the mouse (doc. no. 203-217).
7/1/93	Memo of Record (FDA telephone call)	FDA request for SBA and trade name for TI 211-950 (spirapril hydrochloride) Tablets.
7/2/93	Submission to FDA	Response to trade name request on 7/1/93 submitted "Equaten®" for review.

NDA No. 20-240 [TI 211-950 (spirapril hydrochloride) Tablets]		
7/7/93	Memo of Record (FDA telephone call)	FDA request for revised draft labeling for sample container/carton labels featuring the trade name "Equaten®"
7/22/93	Submission to FDA	Submitted Draft Summary Basis of Approval.
8/9/93	Memo of Record (FDA telephone call)	Trade name "Equaten®" is acceptable.
8/23-26/93	Memo of Record (FDA telephone call)	Request to FDA to keep drug synthesis information confidential and to therefore, create drug master file.
9/3/93	Memo of Record (FDA telephone call)	Request to FDA on acceptability of a 3 mg. dosage strength and for Division to issue Approval letter instead of Approvable letter.
9/8/93	Memo of Record (FDA telephone call)	Request to submit data to support updating the expiration date for the TI 211-950 Tablets from 2 years expiration dating to 4 years.
10/7/93	Submission to FDA	Submission of seven diskettes with data sets for six studies that monitored ambulatory blood pressure.
10/12/93	Memo of Record (FDA telephone call)	Follow-up to 3 mg dosage strength acceptability and status of secondary review by Dr. Lipicky.
10/18/93	Submission to FDA	Resubmission of diskettes mentioned above in DOS version 6.03.
10/29/93	Memo of Record (FDA telephone call)	Status of secondary review timelines by Dr. Lipicky and FDA acknowledgement that the Sandoz request for a drug master file for the drug synthesis information was still under review.
11/10/93	Memo of Record (FDA telephone call)	FDA request for validation information on the analytical methods of TI 211-950 (spirapril hydrochloride) Tablets.
11/12/93	Memo of Record (FDA telephone call)	Point-by-point response to FDA request for validation information per 11/10/93 telephone call.

NDA No. 20-240 [TI 211-950 (spirapril hydrochloride) Tablets]		
11/17/93	Memo of Record (FDA telephone call)	Further response to FDA request for validation information per 11/12/93 telephone call.
12/1/93	Memo of Record (FDA telephone call)	Follow-up on status of Dr. Lipicky secondary review and resolution of drug master file/drug synthesis information issue.
12/15/93	Memo of Record (FDA telephone call)	Revisit status of Dr. Lipicky secondary review.
1/13/94	Memo of Record (FDA telephone call)	Secondary review still progressing, draft labeling to be forwarded to Sandoz.
2/2/94	Memo of Record (FDA telephone call)	Secondary review completed, application to Dr. Temple, draft labeling, submission of new trade name Renormax®.
2/17/94	Memo for Record (FDA telephone call)	Request for FDA to forward to Sandoz additional completed reviews, contents of approvable letter discussed.
2/17/94	Submission to FDA	Letter explaining that Roberts Pharmaceutical Corporation has no rights to the product and that Marion Merrell Dow Incorporated is the new licensing partner.
2/22/94	FDA Letter	Copy of the secondary review performed by Dr. Lipicky.
3/7/94	Memo for Record (FDA telephone call)	Notification to FDA that Environmental Assessment will be amended to replace Roberts Phamaceuticals information with Marion Merrell Dow information.
4/11/94	FDA Letter	Class labeling changes for all ACE inhibitors, incorporation needed into Renormax® labeling.
5/17/94	Memo for Record (FDA telephone call)	Status of Dr. Temple review of Renormax®.
6/3/94	Submission to FDA	Submission of revised Environmental Assessment.

NDA No. 20-240 [TI 211-950 (spirapril hydrochloride) Tablets]		
6/9/94	Memo for Record (FDA telephone call)	Status of Dr. Temple review of Renormax®.
6/29/94	Memo for Record (FDA telephone call)	Status of Dr. Temple review of Renormax®.
7/21/94	FDA Letter	FDA question in regard to completed review of methods validation.
7/25/94	Memo for Record (FDA telephone call)	Identify to FDA that the methods validation response from Sandoz is expected to be submitted within a couple of weeks.
8/4/94	Memo for Record (FDA telephone call)	FDA request for information in regard to the incidence of cancer in Renormax® treated hypertensive patient population and any other patient population studied with Renormax®. Also requested FDA to advise Sandoz on use of auto titration analyzer versus HPLC methodology in methods validation of Renormax®.
8/8/94	Submission to FDA	Submission of point-by-point response to FDA methods validation questions.
8/9/94	Memo for Record (FDA telephone call)	Dr. Temple identifies status of his final review for Renormax®.
8/9-10/94	Memo for Record (FDA telephone call)	Received telefax from FDA requesting patient exposure information/clarification of request.
8/12/94	Submission to FDA	Submission of replacement pages for methods validation submission of 8/8/94.
8/29/94	Submission to FDA	Submission of patient exposure information.
9/6/94	Submission to FDA	Submission of more patient exposure information.
9/15/94	Submission to FDA	Submission of batch production and control records.

NDA No. 20-240 [TI 211-950 (spirapril hydrochloride) Tablets]		
9/26/94	FDA Letter	FDA request to use data from Renormax® in a meta-analysis to examine the safety of placebo controlled trials.
11/1/94	Submission to FDA	Response to FDA Letter for use of data from Renormax®.
11/3/94	Memo for Record (FDA telephone call)	Status of Dr. Temple review of Renormax®.
11/28/94	Memo for Record (FDA telephone call)	FDA identifies seven questions in regard to their review of the Renormax® Environmental Assessment.
11/28-30/94	Memo for Record (FDA telephone call)	FDA identifies that Dr. Temple has completed his review of Renormax® and itemizes other data that Dr. Temple has reqested. Also FDA requests that Sandoz meet with them to discuss Dr. Temples requests for further information (postmarketing studies/non-mem analysis).
12/2/94	Memo for Record (FDA telephone call)	FDA explains that meeting with Sandoz is last step before approvable letter can be issued.
12/6/94	Submission to FDA	Submission of point-by-point response to FDA Environmental Assessment questions.
12/8/94	FDA/Sandoz Meeting	Meeting with FDA to address Dr. Temple's requests for further information and to discuss Dr. Temple's package insert comments on Renormax®.
12/14/94	FDA Letter	FDA additional questions on submission of 12/6/94.
12/21/94	Submission to FDA	Submission of Freedom of Information copy of Environmental Assessment and draft labeling of package insert.
12/23/94	Submission to FDA	Submission of Revised draft package insert and a point-by-point response to the FDA requests for further information in regard to the Clinical Pharmacology section of the package insert.

NDA No. 20-240 [TI 211-950 (spirapril hydrochloride) Tablets]		
12/29/94	FDA APPROVAL Letter	Receipt of the FDA APPROVAL Letter (dated 12/29/94) for Renormax® Tablets NDA 20-240.